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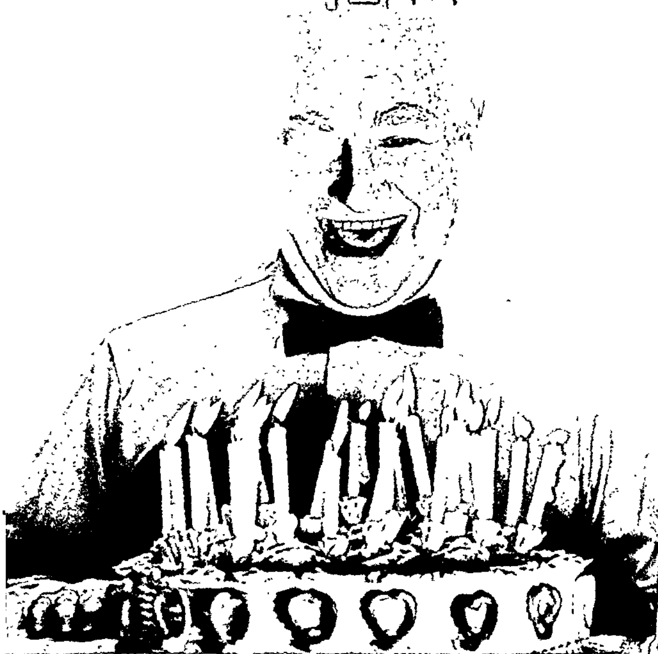
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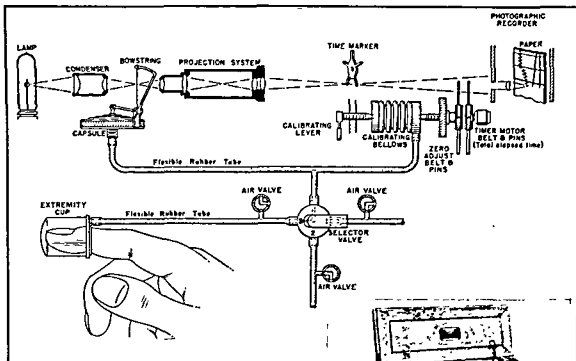
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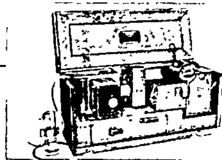
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American Heart Journal

July, 1962, Volume 64, Number 1

Editorial

A critique of certain measures presently employed in managing patients with cardiac infarction

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The opening couplet of Pope's *Epistle to Allen Lord Bathurst*, written early in the eighteenth century, reads as follows:

> Who shall decide, when Doctors disagree,
> And soundest Casuists doubt, like you and me?†

These lines will serve as my text. And let me call attention to the words "presently employed" in the title of this limited review. They were included with intent, in order to stress the rapidity with which advances in scientific knowledge render obsolete many therapeutic practices which are highly regarded in their time, but which are superseded, in turn, by others which undergo a similar fate. Particularly during the past half century, there have been radical changes in our concepts of management, both medical and surgical, in the domain of cardiovascular diseases.

To win approval of its merit, any form of therapy should: (1) be based on sound physiologic principles; (2) demonstrate its effectiveness by controlled clinical trial, carried out by *trained investigators*, over a sufficiently long period of time; (3) establish its freedom from harmful side actions, both immediate and remote. However, exception to the last criterion may be made under special circumstances which justify assumption of a calculated risk.

The discussion which follows is designed to be provocative rather than dogmatic. To pass final judgment, at this time, on the measures to be considered is not warranted, for interpretation of incomplete knowledge, even by competent observers, leads to the expression of conflicting views. There are numerous reasons why a just appraisal is hard to make. Among these are: (1) uncertainty as to the prime causes of atherosclerosis, which is responsible for over 95 per cent of the cases of coronary artery disease; (2) errors in clinical diagnosis with respect to the specific anatomic lesions in the heart; (3) variability in the spontaneous course of the illness; and (4) faulty use of the statistical method in arriving at conclusions.

Of the various aspects of management of

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†There may be some who are uncertain as to the precise definition of a casuist and who might consider i[t] to consult a dictionary. According to Webster, a casuist is one skilled in resolving [illegible] conduct.

the patient with cardiac infarction, three have been chosen as being topics of spirited controversy. They are *diet, anticoagulants,* and *the smoking of tobacco.* Brief reference to the importance of the proper approach to statistics is added, because of its relevancy.

Diet. Cholesterol has become a household word. A great deal of scientific work, much of it fruitful, has contributed to our knowledge concerning the etiology of atherosclerosis. The role of cholesterol, as well as that of other lipid substances, is discussed at length in medical journals, magazines for the laity, and the daily press. Even the *Wall Street Journal,* in a recent issue, headed its leading article: "Helping the Heart; Major Research Effort Started to See if Diet Can Prevent Heart Attacks." Doctors are plagued by patients who want to know their cholesterol level and clamor for diets, as well as medications, which will lower it. Advertisements for liquid corn oil and corn oil margarine strike the eye. Saturated and unsaturated fats have become subjects for dinner table chit-chat. Radical changes in the eating habits of an entire nation have been suggested by its government: the National Board of Health of Sweden recently recommended for the people of that country a general restriction in fat intake and, for "susceptibles,"[1] a shift toward polyunsaturated fats.[2] By way of contrast, Morris[3] states that "a tentative investigation by our research unit in England so far has shown no association whatsoever in the individual, at current levels of consumption, between what is known of habitual caloric or fat intake and casual blood lipid levels." Our own National Heart Institute is about to launch an extensive program to determine whether cholesterol-lowering diets can be made sufficiently palatable to be accepted by the American public, and, if so, whether their use, over a period of 5 or 10 years, would influence favorably the incidence of coronary heart disease.

What is the meaning of all this furor? What is its immediate importance to the physician and the patient? At the present time, the established facts are few. There appears to be a statistical relationship between the amount of cholesterol and other fats in the blood and atherosclerotic heart disease. It is possible, by limiting the intake of fat in the diet, whether saturated or unsaturated, to lower the amount of serum cholesterol. Certain drugs tend to decrease the level of cholesterol, particularly in the presence of hypercholesterolemia. But the important fact is that, as yet, no sound evidence exists to show that diminishing the amount of cholesterol in the blood will reduce the incidence of either coronary sclerosis or cardiac infarction. Furthermore, other dietary factors, such as the amount and kind of carbohydrate eaten, as well as the amount of protein, may play a part in altering the levels of cholesterol.[4]

In addition to diet, many conditions and circumstances have been under suspicion as contributory causes of atherosclerosis. The list includes heredity, race, anthropologic characteristics, economic status, emotional stress, lack of exercise, obesity, hypertension, and excessive use of tobacco. Among the victims of cardiac infarction, the male sex and older persons certainly predominate. Specific diseases, such as diabetes mellitus and hypothyroidism, appear to exert a predisposing influence. It is highly probable that multiple etiological factors are concerned.

To lower the level of cholesterol in the blood to a significant degree by dietary restriction requires rigid observation of the rules and the elimination of numerous items which make foods tasty. Moderate curtailment accomplishes little or nothing, although it may quiet the conscience of the physician and satisfy the demands of the patient. Books and pamphlets which contain recipes for low-fat meals abound, but not every housewife is able or willing to follow a strict regimen in the kitchen, particularly since there is no assurance that the desired aim will be accomplished. On the other hand, in the obese, reduction in weight, carried out under proper guidance and with the cooperation of the patient, is a feasible undertaking and is of unquestionable benefit.

A number of substances have been tried in the effort to lower blood cholesterol, but, for various reasons, none has been successful or practical. Of the drugs which have been employed for this purpose, triparanol (MER-29), a widely advertised product, deserves special mention. It apparently

inhibits the synthesis of cholesterol by preventing the conversion of desmosterol, its immediate precursor, into cholesterol; whether substitution of desmosterol for cholesterol represents a forward step is open to question. Early reports have indicated that triparanol does decrease elevated concentrations of cholesterol in the blood of some patients.[5] Mild side actions, such as headache, nausea, and a variety of cutaneous rashes, have been noted. Alopecia and ichthyosis have been reported.[6] But of vital clinical importance have been the adverse effects of a more serious nature, to which attention was called in a circular letter sent to physicians by the manufacturers.* Among those described in patients were formation of cataracts, depression of adrenocortical function, abnormal tests of liver function, and leukopenia. In laboratory animals, administration resulted, in some instances, in sterility, abortion, damage to the liver, diminished spermatogenesis, and, in dogs, acute intravascular hemolytic episodes and even death.

This experience affords a striking example of premature promotion of a therapeutic agent by a pharmaceutical firm. Acknowledgment of error is praiseworthy, but it does not compensate for damage already done. Because the grave toxic effects of this drug far outweigh any possible beneficial actions, triparanol should be withdrawn from the market and its use promptly discontinued.

It seems reasonable to say, then, on the basis of known facts, that a radical change in the dietary habits of all persons in the United States is not now justified. The consumption of fats in this country is indeed high. Perhaps, until further investigation has thrown more light on the problem, there should be moderate curtailment of the intake of fats by the general population, with reasonable substitution of polyunsaturated for the saturated variety. Such procedure is suggested, without guarantee, as a *possible* means of preventing atherosclerosis or retarding its course, if already present. This, in essence, has been the recommendation of the Ad Hoc Committee on Dietary Fat and Atherosclerosis of the American Heart Association.[7] For the immediate present, it behooves the medical profession not to impose needlessly rigid restrictions on "susceptibles" or on patients who have manifested frank symptoms of cardiovascular disease.[8] This policy applies particularly to elderly persons, who, perforce, are no longer able to enjoy some of the pleasures of youth but who can still appreciate good cooking.

Anticoagulants. Reports which deal with the results of anticoagulant therapy in the treatment of cardiac infarction are legion, both in this country and abroad. Their tone has ranged from enthusiasm[9] to denunciation.[10] The remarks which follow apply only to the use of coumarin derivatives, with which the largest experience has been accumulated. But before proceeding with therapeutic considerations, a few words concerning accuracy of diagnosis are pertinent.

In a review of the clinical and autopsy records of 500 patients with cardiac infarction who died in Barnes Hospital, in St. Louis, Lee and associates[11] found that an incorrect antemortem diagnosis was made in 19 per cent. Capeci and Levy[12] made a similar correlation in 100 cases of pathologically proved cardiac infarction at the Presbyterian and St. Luke's Hospitals, in New York. Infarction was not recognized in 20 per cent; the clinical diagnosis of infarction was not confirmed in 14 per cent. The over-all diagnostic error was 18 per cent. At the Boston City Hospital, Ellis and his associates,[13] in 101 cases studied at autopsy by an injection technique, noted that 40 per cent of pathologically proved cardiac infarctions were not recognized clinically. False diagnoses were made in 14 per cent. The over-all error was 33 per cent. In the records of 266 cases of infarction examined at autopsy at the Royal Infirmary in Edinburgh, by Paton,[14] the clinical diagnosis was incorrect in 56 per cent. These figures are significant and surprising. Evaluation of the effectiveness of treatment, if directed against the wrong disease, can hardly be accepted as valid.

In cases of acute infarction, some observers have attributed the favorable effect of the anticoagulant to reduction of the incidence of intracardiac thrombi and sys-

*This letter, dated Dec. 1, 1961, came from the Wm. S. Merrell Company, Cincinnati, Ohio, and was headed "Drug Warning—MER/29."

bly the British,[15,16] deny this claim. They assert that because there have been fewer instances of pulmonary infarction, both mild and fatal, in their treated cases, the action has been on the peripheral venous system; in other respects, they found no difference between treated and untreated cases. In our own series[12] there was no important difference, at autopsy, in the incidence of thromboembolism in the treated group and in the controls. A similar experience was noted by Waldron and associates[17] at the Massachusetts General Hospital.

In four municipal hospitals in Copenhagen, 1,404 patients with cardiac infarction were studied between the years 1954 and 1958; the results were reported, after painstaking analysis, in 1961.[18] In their summary, the authors state bluntly: "The conclusion must be that anticoagulant therapy is not indicated in acute myocardial infarction."

The benefits to be derived from long-term administration of an anticoagulant have been extolled in numerous reports. The British Medical Research Council,[19] in preliminary analysis of the results obtained in 300 selected patients, concluded that, in the conditions of this trial, such therapy "can make a useful if limited contribution to the after-care of patients who have recovered from the acute phase of myocardial infarction." On the basis of a review of published data which totaled over 5,000 cases, McMichael and Parry,[20] of London, have taken issue with the conclusions of the Council. It is their opinion that, despite many claims, the evidence that long-term anticoagulant prophylaxis, as carried out today, prevents recurrence or reduces mortality after the acute attack is still inadequate. Bjerkelund,[21] in Oslo, has taken an intermediate position. He believes that long-term treatment in *all* patients, for the rest of their lives, is not justified, and that such an undertaking would be practically and economically impossible. More would be accomplished by treating, for 6 months, all patients or a number of young patients who have had only one infarct. Clearly, there is need for reconciliation of such diverse judgments.

The risk of hemorrhage is real. It has been observed in almost every organ and tissue in the body, occurring, occasionally, when prothrombin levels have been within the prescribed limits of safety. It may be slight and readily controlled, or massive and sometimes fatal. Its incidence has varied, in different series, from 9 to 27 per cent. In the patients who died, it was not infrequently unrecognized, antemortem, as the cause of death.

Cardiac rupture is another grave complication. In 796 cases collected from the literature by Capeci and Levy,[12] of which 557 were not treated and 239 were adequately treated, proved rupture occurred in the untreated in 3.9 per cent and in the treated in 12.1 per cent. This is a ratio of 3 to 1. The same ratio was observed in the Danish series[18] with respect to hemorrhagic pericardial effusion without rupture.

In the light of conflicting opinion, what stand should the physician take? As in the case of diet, the lay public is aware of anticoagulant therapy, and he who refrains from prescribing it is subject to blame if the course is unfavorable. Should hemorrhage or cardiac rupture occur, the responsibility likewise is his. As of now, decision as to the course which the physician chooses to follow must rest with him.

Smoking. No one will deny that there are many persons who derive pleasure and emotional satisfaction from smoking tobacco. In his delightful book entitled, *My Lady Nicotine*, Sir James Barrie says, in referring to his favorite pipe mixture: "It clears the brain and soothes the temper." It is common practice to advise every patient with coronary heart disease to abstain from the use of tobacco. But there is disagreement as to the necessity of such deprivation under all circumstances; and whether nicotine plays a part in causing this disorder is still a matter of debate.[22]

Several years ago, studies were made in our laboratory on the effects on the heart of smoking cigarettes. Observations included changes in heart rate and blood pressure, alterations in the form of the electrocardiogram, and variations in cardiac output as determined by the ballistocardiograph.[23] The results may be summarized as follows: there was, on the average, a slight rise in heart rate and blood pressure, in both normal persons and patients with heart disease. In neither group

was there a significant increase in cardiac output. There was a considerable range of variation in both groups, in all of these categories. Slight changes in the form of the electrocardiogram occurred in less than half of the subjects in each group. "Tobacco angina" was extremely rare, even in those subject to spontaneous attacks. In a few persons in whom angina occurred after smoking, transient electrocardiographic changes similar to those seen in cardiac infarction have been recorded by Wilson[24] and others; these changes have been attributed to spasm of the coronary arteries.

It is the nicotine which produces the cardiovascular effects,[25] and these are increased by inhalation of the smoke. Decreasing the amount of nicotine in cigarettes reduces the degree of response, but does not entirely eliminate the reaction.[26] Drinking a cocktail will not nullify the effects of smoking a cigarette.[27]

In my opinion, except for persons known to react badly to nicotine, those who are dependent on smoking for curbing their emotions (or think this is so) may be permitted to smoke in moderation; this is taken to mean 10 cigarettes in 24 hours. The harm in excessive smoking should be stressed. The use of tobacco is strictly forbidden for at least 4 months after an episode of acute cardiac infarction. There should be no smoking in the presence of congestive failure. Peripheral vascular disease is an indication for permanent abstinence.

Statistics. With increasing frequency, the results of medical investigations are being submitted to statistical analysis. Most physicians are untrained in the science of statistics and, as Mainland[29] has pointed out, "the thorough application of statistical thinking to the design, performance, and analysis of an investigation is an art in which even experienced practical statisticians make mistakes. *A fortiori*, even a senior research worker, if he has previously done nothing with statistical techniques except apply tests, is likely to go astray, even in apparently simple projects, unless he is willing to be guided in planning and conducting his investigation by someone (whether labeled 'statistician' or not) who is truly able to guide him."

In the study of a disorder such as atherosclerotic heart disease, which is subject to so many variables, "perversion of statistics," to use Mainland's term, can readily lead to false conclusions. It seems possible that some of the differences in opinion, to which reference has been made, may be attributed to this type of error.

What has been said represents an attempt to present a point of view. I shall conclude with two quotations, for they bring sharply into focus thoughts bearing upon the preceding remarks and, I trust, implied in them.

The first quotation is taken from Morris West's recent novel, *Daughter of Silence*. The speaker is a distinguished psychiatrist: "I think it's true of all sciences that the great leaps of discovery have been made by bold speculators whose very errors have served in the end to elicit another fraction of the truth."

The second quotation, a favorite of Sir William Osler, is by Cowper:

> Knowledge and wisdom, far from being one,
> Have oft-times no connexion. Knowledge dwells
> In heads replete with thoughts of other men;
> Wisdom in minds attentive to their own.
> Knowledge is proud that he has learned so much;
> Wisdom is humble that he knows no more.

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Clinical communications

Some observations on the relationships between atherosclerosis, hyperlipemia, and D-thyroxine

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Chicago, Ill.

Atherosclerosis, which is perhaps the most universal form of lethal pathology in our society, stimulates clinical concern only when it attains some observable threshold, e.g., angina pectoris, myocardial infarction, or a cerebrovascular catastrophe. Atherogenesis, i.e., those causes and processes which lead to atherosclerosis and ultimately to infarction, may be as severally disposed and protean in anlage as the vast, and at times speculative, literature would indicate. In any case the pathologic primordia and the definitive course of atherogenesis are still largely unknown. The factors[1-3] which encourage the propensity to the earliest proliferative changes in the artery (atherogenesis) must be differentiated from those processes (e.g., lipid infiltration) which enhance an ongoing atherosclerosis or promote recurrent infarction. There is a large body of evidence[4-10] which suggests that hyper-β-lipoproteinemia or hypercholesterolemia are conducive to increased arterial pathology. The origin (diet, metabolic precursors) and precise nature of these pathogenic serum lipids is imperfectly described.

Throughout the recent past, various authorities have advocated a large array of decholesterolizing and lipemia-clearing substances. More than occasionally, data from animal research were extrapolated as evidence of quality in man. At other times, metabolic, emotional, thrombolytic, and other untoward responses were minimized in the search for lipemia-lowering agents. Investigators gave considerable attention to lipotropic agents, thyroid, estrogen, and heparin among others. Choline, inositol, methionine, pyridoxine, and other lipotropic agents were found to have minimal lipid-lowering potential in man.[11] Estrogenic substances, whatever their effect on serum lipids, exerted so profound a psychosexual influence as to obviate their utility. Corroboration of the reported cholesterol-lowering response to heparin has been incomplete, and the jeopardy to the clotting mechanism is constant. Thyroid hormone was reported[12] to be capable of inhibiting atherosclerosis in the animal and lowering blood cholesterol. The inhibition of atherogenesis was noted in several animal species, and the decholes-

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Atherosclerosis, which is perhaps the most universal form of lethal pathology in our society, stimulates clinical concern only when it attains some observable threshold, e.g., angina pectoris, myocardial infarction, or a cerebrovascular catastrophe. Atherogenesis, i.e., those causes and processes which lead to atherosclerosis and ultimately to infarction, may be as severally disposed and protean in anlage as the vast, and at times speculative, literature would indicate. In any case the pathologic primordia and the definitive course of atherogenesis are still largely unknown. The factors[1-3] which encourage the propensity to the earliest proliferative changes in the artery (atherogenesis) must be differentiated from those processes (e.g., lipid infiltration) which enhance an ongoing atherosclerosis or promote recurrent infarction. There is a large body of evidence[4-10] which suggests that hyper-β-lipoproteinemia or hypercholesterolemia are conducive to increased arterial pathology. The origin (diet, metabolic precursors) and precise nature of these pathogenic serum lipids is imperfectly described.

Throughout the recent past, various authorities have advocated a large array of decholesterolizing and lipemia-clearing substances. More than occasionally, data from animal research were extrapolated as evidence of quality in man. At other times, metabolic, emotional, thrombolytic, and other untoward responses were minimized in the search for lipemia-lowering agents. Investigators gave considerable attention to lipotropic agents, thyroid, estrogen, and heparin among others. Choline, inositol, methionine, pyridoxine, and other lipotropic agents were found to have minimal lipid-lowering potential in man.[11] Estrogenic substances, whatever their effect on serum lipids, exerted so profound a psychosexual influence as to obviate their utility. Corroboration of the reported cholesterol-lowering response to heparin has been incomplete, and the jeopardy to the clotting mechanism is constant. Thyroid hormone was reported[12] to be capable of inhibiting atherosclerosis in the animal and lowering blood cholesterol. The inhibition of atherogenesis was noted in several animal species, and the decholes-

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terolizing response was reported by several investigators.[7,8,13,14] Unfortunately, the pharmacologic and metabolic side effects of thyroid hormone were not consistent with continued usage. Recently, attention has been given to some of the isomers of thyroxine, and potent cholesterol-lowering responses have been noted.[15-21]

The lowering of serum lipids, especially the beta-lipoprotein fraction which transports cholesterol, is widely considered to be an important clinical goal which may ameliorate the morbidity of the atherosclerotic process. Because of the lipid nature of atheromata and the weighty, if inconclusive, literature, the search for nontoxic, lipemia-clearing agents seems to be worth while.

This communication deals with the pharmacologic development and clinical investigation of the D-isomer of thyroxine, the pharmacology of which is herewith summarized.

1. D-Thyroxine has one tenth the calorigenic activity of L-thyroxine (the active principle in human physiology) in the mouse and one fortieth of the same effect in the rat as measured by oxygen consumption.[22]

2. Goiter-suppressant activity (produced by propylthiouracil) of D-thyroxine in the rat is one fourth that of the L-isomer.[22]

3. Metamorphosis of the tadpole was accelerated by D-thyroxine with approximately one half the potency of the L-form.[22]

4. L-Thyroxine stimulates rate and weight changes in the myocardium with 100 times the potency of the D-isomer. The lipemia-clearing dose of D-thyroxine is, however, very much lower than the pulse-increasing dose.[19]

5. D-Thyroxine stimulates hepatic oxidative catabolism and excretion of cholesterol and its degradation products via the bile and bowel in the feces.[8]

6. In addition to the foregoing, the D- and L-forms have different rates of concentration in vital organs and removal from blood.[5]

7. The D-form is excreted almost completely in the urine and feces.[5]

8. In hypothyroid patients the D-isomer has one tenth to one fiftieth the potency of the L-form.[23]

9. Toxicologic studies of the D-form in several species in the laboratory indicated that its general safety might be expected in man.[7,8,14,15]

Methodology

For this study, 239 adult Caucasians, of both sexes, were selected. They ranged in age from 30 to 65 years. Although elaborate evaluation of the diet was not undertaken, the diet was largely unchanged throughout the course of the study. Patients who simultaneously received female sex hormones or other drugs were not considered statistically, nor were those patients who were studied for less than 2 months. Determinations of cholesterol were made under standardized laboratory conditions, and the study group consisted of more than 12 ethnic subcultures. In the final analysis, there is much to impede the formation of judgments because of the many sources of error cited above. Therefore, we attempted to randomize our sample and to study the following: (a) mean terminal change in the concentration of serum cholesterol as determined by the Liebermann-Burchard reaction; (b) endocrinologic and somatic responses; (c) toxicologic data in a large series of patients studied for long periods of time; (d) influence on the electrocardiogram; and (e) two comparative groups—one treated with niacin, and the other with estrogenic substances.

The dose of D-3,5,3′,5′-tetraiodothyroxine (D-T_4)* initially was 8 mg. per day. However, our preliminary studies indicated that doses up to 16 mg. per day did not exhibit metabolic effects. Neither angina pectoris nor other cardiac aberration was noted in the entire study period. Serial electrocardiographic studies carried out on approximately 100 patients for 3 months failed to reveal any single instance of change traceable to D-T_4. Although not a substitute for rigid controls, we have employed several "anti-atherosclerosis," decholesterolizing agents, including 5,3′-triiodothyroxine (D-T_3), heparin, the lipo-

*Supplied for this study as Choloxin, brand of sodium D-3,5,3′,5′ tetraiodothyroxine, Baxter Laboratories, Inc., Morton Grove, Ill. The authors gratefully acknowledge the helpful assistance of Thomas A. Garrett, M.D., Medical Director, Baxter Laboratories, Inc., who supplied this compound for our study.

tropic agents (choline, inositol, methionine, and pyridoxine), progesterone,[21] and placebos. Nicotinic acid and an orally active form of conjugated estrogens were used in this study. The lipotropic agents, as has been established in many studies, produce only meager changes in serum cholesterol. Nicotinic acid frequently produces hyperglycemia and extensive vasodilation. D-T_3 has a greater propensity than D-T_4 to produce thyroxine-like metabolic changes when hypocholesterolemic doses are employed. In our hands, a preliminary study with D-T_3 in 5 patients (mean basal cholesterol of 300 mg. per cent) revealed a much less (average drop of 55 mg. per cent in 8 weeks) impressive decholesterolizing response than did D-T_4 (average drop of 105 mg. per cent in 8 weeks).

Although we made an effort to study and standardize pretherapy lipid levels, and undertook to control and rule out extraneous influences, we are very much aware of the limitations of our data and conclusions. Nevertheless, the observations noted were gained from a large study group (239), and over a considerable period of time (8 weeks). The average decrement in the level of cholesterol was 105 mg. per cent. In extreme hyperlipemia the lowering of cholesterol was often more dramatic. Even if this occasional potency is disregarded, the study seems to support the conclusion that D-T_4 is a dependable and safe drug. Moreover, after the first sharp decline in serum cholesterol, the level was maintained even after reduction of dosage to 4 mg. per day.

In a subgroup of 55 patients in whom treatment had proceeded for 1 month and the maximum decholesterolizing effect was achieved (a decrease of −96 mg. per cent), treatment was stopped and studies of blood levels were continued. Within 45 days an average rise of 80 mg. per cent in cholesterol was observed. Pursuant to this spontaneous recurrence of hypercholesterolemia, D-T_4 therapy (8 mg. per day) was reinstated. A second precipitous fall in cholesterol was noted, which paralleled the original drop. Moreover, the new lowered blood level was maintained for 6 months on 4 mg. per day. This corroborating response is submitted as evidence that the normo-cholesterolemia that obtained was not fortuitous but was directly related to the drug employed.

Another subgroup of 50 patients (who received 8 mg. per day) was studied 6 months beyond the average tenure with repeated determinations of serum cholesterol at approximately 6-week intervals. These patients exhibited a similar, somewhat precipitous decrease in the concentration of serum cholesterol early in therapy (an average fall of 95 mg. per cent from an average basal cholesterol of 315 mg. per cent within 8 weeks). Subsequently, there was a gradual decline to an ultimate average of 185 mg. per cent in an average of 3 more weeks. This mean level of approximately 185 mg. was maintained with only 4 mg. per day for 7 months, as determined by four additional determinations of cholesterol.

Results and discussion

Studies on atherosclerosis and on lipid clearance are exceedingly difficult to interpret, even when exhaustive measures to control the gathering of acceptable data are employed. These data demonstrate a high degree of coupling (i.e., relatedness to other biologic, physical, and psychic phenomena and systems) which tends to make the isolation and interpretation of data hazardous. Among the factors which, on the basis of experimental evidence, vitally influence atherogenesis and serum lipids are: age, sex, diet, ethnic background, weight, body type, and other somatic pathology (e.g., endocrinopathy, liver disease, etc.). For example, people who ingest foods high in saturated fatty acids, Americans of Jewish or Italian descent, and patients with pheochromocytoma or hypothyroidism, reportedly exhibit high levels of lipids and a high incidence of atherosclerosis. Therefore, studies with compounds that lower serum lipids must undertake to measure the above-mentioned and other influences which might expand or detract from pharmacologic response.

However, when cautious clinical investigations are carried out with discrete attempts to evaluate and rule out the rol of diet, ethnic background, etc., the predictability and wide variance of

Table I. Response of cholesterol to sodium dextro-thyroxine (D-T_4), nicotinic acid, and estrogen

Patient category	Number of patients	Therapeutic agent	Dosage (mg /day)	Mean serum cholesterol (mg. %) Basal	+5 wk.	+8 wk.	+32 wk.	Incidence of untoward reactions (%)
Hyperlipemia without cardiovascular disease	74	Sodium dextro-thyroxine	8(8 wk.) then 4	306	209	184	181	Less than 3%
Hyperlipemia with cardiovascular disease	130	Sodium dextro-thyroxine	8(8 wk.) then 4					
Hyperlipemia without cardiovascular disease	20	Nicotinic acid	3,000	300	249	—	—	Hyperglycemia 20; Vasodilation 20; Headache 1
Hyperlipemia without cardiovascular disease (males only)	15	Conjugated estrogens	10	310	225	210	—	Psychosexual changes > 50

Table II. Hypocholesterolemic influence of sodium dextro-thyroxine (D-T_4) in 55 patients in whom levels of cholesterol were depressed (subsequent to first administration of D-T_4), re-elevated (subsequent to discontinuance of D-T_4), and depressed for a second time (pursuant to reinstitution of D-T_4)

Patient category	Number of patients	Average age	Basal cholesterol (average of 3 determinations)	D-T_4 (8 mg./day) Cholesterol after 5 wk. (average)	Cholesterol after 8 wk. (average)	Cholesterol after 16 wk. (60 days without treatment)	Cholesterol after 20 wk. with D-T_4 (8 mg./day)	Cholesterol after 83 wk. with D-T_4 (8 mg./day)
Group A Hyperlipemia but without clinically demonstrable cardiovascular disease	20	33	309	213	190	265	201	182
Group B Hyperlipemia with clinically demonstrable cardiovascular disease	35	48						

ineluctably leads to the conclusion that other extremely vital but undiscovered parameters are of nuclear significance. Some of these undiscovered pathogenetic mechanisms which influence serum lipids, hemodynamics, and atheromatosis will undoubtedly be correlated with more subtle, more molecular change in the internal milieu of the artery. Evidence of high-energy phosphate influences in atherosclerosis and medial arteriosclerosis have been reported.[14,25-27] The role of such vital moieties as -SH donors (acetyl coenzyme A, thioctic acid, etc.) needs to be examined further. Perhaps of greater importance, however, is the role of the psychic apparatus in lipid metabolism and atherosclerosis as well as myocardial infarction

and angina pectoris. The coercion contributed by emotional states in provoking hemodynamic change (e.g., vasoconstriction) may be juxtaposed to the unexplained incidence of myocardial infarction seen without atherosclerotic coronary arteries.[28,29] Recently, dietary habits in the chicken were positively correlated to arterial disease. Those chickens which were regular meal eaters showed far greater (seven times) atherosclerosis and hypercholesterolemia than did nibblers with identical diet.[30] It is difficult to control, experimentally, such factors (the method of eating rather than the content of the diet), which suggests a psychologic role.

The data shown in Tables I and II are submitted for consideration and analysis within the interpretative limits structured by the many variables and influences discussed. Because of the concatenation of factors which contribute to the level of serum cholesterol, our *evaluation* of data is guarded. The issue in this study is not a question of the role of hyperlipemia in primordial atherogenesis, nor does it verify or refute the widely held hypothesis that hyperlipemia aggravates extant atherosclerosis. The investigation was undertaken in order to study the biochemical response of serum lipids to a completely new agent that had proved to be extremely efficacious and safe in several animal species. The fact that arteriopathy and lipemia patterns vary from animal to animal makes the versatility and uniformity of the decholesterolizing response that much more germane.

Summary

1. Clinical investigation was undertaken in 239 patients with tetraiodo-D-thyroxine. Exhaustive pharmacologic and toxicologic data are noted which tend to corroborate the results reported here in man.

2. An average decline in serum cholesterol of 105 mg. per cent was induced by a dose of 8 mg. daily and maintained within 35 days. This lowered level was then maintained on a daily dosage of 4 mg. for 6 to 7 months. Untoward reactions never attained serious proportions (induced or heightened angina pectoris or extreme metabolic effect), and the over-all incidence of about 2.5 per cent is noteworthy.

3. With strict reservations as to the etiological importance of hyperlipemia per se, but with an awareness of the role widely suggested for lipids in furthering an extant atherosclerosis, we have submitted these data for consideration.

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Detection of the small intracardiac shunt with the hydrogen electrode. A highly sensitive and simple technique

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The patient with a large left-to-right intracardiac shunt is readily recognized during routine catheterization of the right side of the heart. However, when the left-to-right shunt is less than 20 per cent of systemic flow, oxygen saturations from the right side of the heart may fail to positively identify or localize a left-to-right shunt.

Recently, Clark and Bargeron[1-3] introduced a simplified but extremely sensitive hydrogen–platinum electrode system for detection of left-to-right shunts. They observed that a platinum electrode rapidly develops a significant potential in the presence of hydrogen dissolved in blood. A single breath of hydrogen gas is administered to the patient, and this immediately delivers a high concentration of hydrogenated blood to the left side of the heart. In the presence of a left-to-right shunt the hydrogenated blood from the left side of the heart may be readily detected in the right side of the heart with a platinum electrode. Thus, by positioning a cardiac catheter with a platinum electrode in the main pulmonary artery, one may detect the presence of a left-to-right shunt in a matter of seconds after the start of the catheterization.

The purpose of this paper is to report the usefulness of this technique in establishing the presence of small left-to-right shunts when oxygen saturations are equivocal, and to emphasize the simplicity of the technique as compared to other existing methods.

Materials and methods

Hydrogen curves have been recorded in 100 patients who ranged in age from 17 days to 56 years, and who had a wide variety of congenital cardiac defects.

Catheters have been designed with either a single platinum electrode at the tip or two electrodes; the second electrode is 10 cm. proximal to the tip (Fig. 1). Results with a *multiple* platinum electrode catheter in human subjects have not been reported previously. Sizes 6F and 7F have been found easy to maneuver and permit sampling of blood and adequate

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except for G. K., who had a postoperative tetralogy. The physical examination revealed an abnormally loud pansystolic murmur, usually maximal in the third left intercostal space, except for Patients C. C., L. D., and G. K., in whom the murmur was shorter and ejection in type, suggesting obstruction. In general, the electrocardiograms were normal. C. C., who was shown to have mild pulmonary stenosis plus a small ventricular septal defect, had possible right ventricular hypertrophy. L. D. had true left axis deviation. G. K., who had the postoperative tetralogy, had the expected right ventricular hypertrophy, both by electrocardiographic and x-ray evidence. The cardiac series could be interpreted as normal, although in some patients there was slight prominence in the area of the main pulmonary artery.

Catheterizations (Table I) revealed increases in oxygen content between the right atrium and the pulmonary artery of .60, .76, .68, .42, .26, and .55 volumes

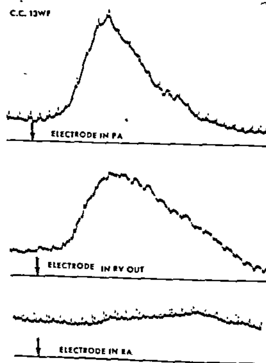


Fig. 3 Small ventricular septal defect. Hydrogen curves using a No 6F 100-cm. catheter with single lumen and one platinum electrode at tip. The arrow indicates inhalation of hydrogen. Early appearance is clearly noted at the ventricular level.

per cent. These values were all within the normal range of variation; hence, no definite diagnosis of a left-to-right shunt was possible on the basis of the oxygen contents.[6-8] However, positive hydrogen curves obtained in each of these patients established the presence of a ventricular septal defect. Representative curves obtained from Patients C. C. and C. W. are shown in Figs. 3 and 4 (*A* and *B*). Therefore, in each of these patients in whom the less sensitive technique of oxygen contents was equivocal the more sensitive technique of hydrogen established the presence of a ventricular septal defect. The ventricular septal defect in G. K. appeared to have been closed at the time of operation; however, the hydrogen curves revealed that the defect was still partially open. The usefulness of hydrogen curves in evaluating congenital heart defects after surgical repair is evident.

B. Small patent ductus arteriosus. R. Y., a 5-year-old asymptomatic Indian boy, was evaluated because of a soft continuous murmur, maximal in the second left intercostal space at the mid-clavicular line. The electrocardiogram was probably within normal limits. The cardiac series suggested a slight prominence of the aorta. Cardiac catheterization revealed: (1) a mild coarctation of the left pulmonary artery, with a pressure of 34/11 mm. Hg in the main pulmonary artery and 18/9 mm. Hg in the proximal left pulmonary artery; and (2) an insignificant jump in oxygen content of .21 volumes per cent at the level of the pulmonary artery. The subsequent recording of positive hydrogen curves from the pulmonary artery established the presence of a small left-to-right shunt, most likely a patent ductus arteriosus (Fig. 5).

C. Small atrial septal defect. The clinical findings in R. S. were unremarkable except for the cardiac series, which revealed a prominent main pulmonary artery with minimal increase in the vascular markings. The electrocardiogram (Fig. 6) was within normal limits. A diagnosis of small atrial septal defect, secundum type, was considered unlikely since this degree of left-ward axis has rarely been seen in over 300 patients with atrial septal defects ... ated in this Center. The oxygen

Table I. Catheterization data

Patient	Right atrium		Right ventricle		Pulmonary artery		Brachial artery		Pulmonary a-v O_2 diff. (vol. %)	Systemic a-v O_2 diff. (vol. %)
	Content (vol. %)	Saturation (%)	Content (vol. %)	Saturation (%)	Content (vol. %)	Saturation (%)	Content (vol. %)	Saturation (%)		
Small Ventricular Septal Defects										
1. C.C. 13, F	11 44	69 7		73*	12 04	73.3	15.07	91 1	3 03	3.63
2. (a) C.W. 9, F	12 88	71 0	13 81	76 4	13 89	76.9	17 40	95 6	3.51	4.52
(b) C.W. 16, F	14.15	73 0	14.18	73 3	14 91	77.1	18 05	92.6	3.14	3.90
3. R.J. 9, M	13.00	67 4	13 55	70 3	13 68	71.0	17.27	88.9	3.59	4.27
4. D.K. 7, M	10 34	70 3		71 0*	10 76	73 1	13 77	92 7	3.01	3 43
5. G.K 6, M	10 32	59 7	10.98	63 5	10 87	62 9	15 76	90 5	5 86	5 44
6. L.D. 3, M	11 35	63 3	11.73	65 4	11.61	64 7	16.73	92.7	5.12	5.38
Small Patent Ductus Arteriosus										
R Y. 5, M	10 21	65 1	10 20	65 0	10.41	66.3	15 06	95 3	4 65	4.86

*By oximeter

at catheterization were equivocal, with but a difference of .46 volumes per cent between the mixed caval samples and the pulmonary artery (Table II). The recording of a positive hydrogen curve from the right atrium established the diagnosis of a small atrial septal defect (Figs. 7, *A* and *B*). In addition, the catheter was advanced across the atrial septum.

Table II. Catheterization data in Patient R. S., 13-year-old boy with small atrial septal defect

	Content (vol. %)	Saturation (%)
Inferior vena cava	14 10	78 7
Superior vena cava	12.53	69.9
Right atrium	14.46	79 8
Right ventricle	13.96	77.9
Pulmonary artery	14 04	78 3
Brachial artery	17 12	94 7

Pulmonary arteriovenous oxygen difference: 3 08 vol. %
Systemic arteriovenous oxygen difference: 3.54 vol. %

D. Negative hydrogen curves. In Patient L. S. the clinical findings were a large left-to-right shunt at the ventricular level. However, the presence of left axis deviation on the electrocardiogram raised the possibility of an endocardial cushion defect with both ventricular and atrial septal defects. Oxygen contents at catheterization confirmed the presence of a large ventricular septal defect with no evidence of an atrial septal defect. To definitely rule out an atrial septal defect, hydrogen curves were recorded; these demonstrated the absence of a left-to-right shunt at the atrial level but confirmed the presence of a ventricular septal defect. Thus, this patient is representative of the small group of patients who have ventricular septal defects with left axis deviation.

D. L. was asymptomatic with normal physical findings. He was referred for evaluation because of a prominence in

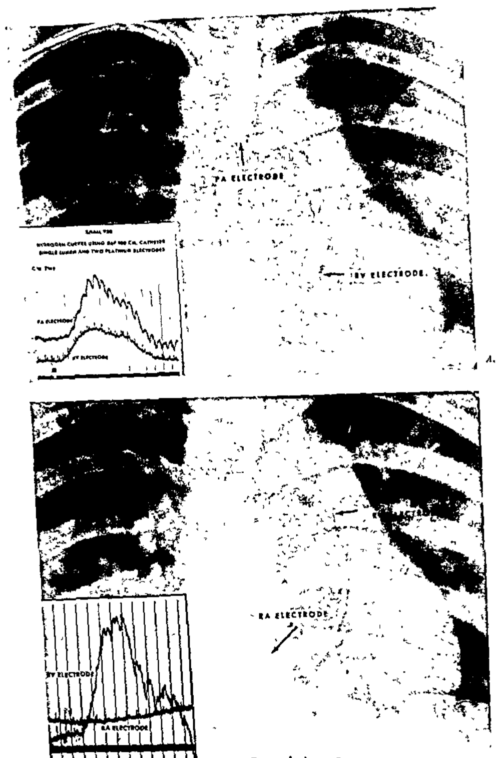


Fig. 4. *A*, Film shows position of catheter electrodes when curves shown in insert were recorded. Early appearance of hydrogen is clearly shown at right ventricular and pulmonary artery electrodes. Note earlier appearance at right ventricular electrode. Recirculation is present on downslope. Inhalation of hydrogen is noted by base-line marker. Electrodes can be easily seen on film. Time lines 1 second apart. *B*, Clearly shows early appearance at right ventricular electrode, but not at right atrial electrode, thereby lo-izing shunt at ventric…

Table I. *Catheterization data*

Patient	*Right atrium*		*Right ventricle*		*Pulmonary artery*		*Brachial artery*		*Pulmonary a-v O_2 diff.*	*Systemic a-v O_2 diff.*
	Content (vol. %)	*Saturation (%)*	*Content (vol. %)*	*Saturation (%)*	*Content (vol. %)*	*Saturation (%)*	*Content (vol. %)*	*Saturation (%)*	*(vol. %)*	*(vol. %)*
Small Ventricular Septal Defects										
1. C.C. 13, F	11.44	69.7		73*	12 04	73 3	15.07	91 1	3 03	3.63
2. (a) C.W. 9, F	12 88	71 0	13 81	76 4	13 89	76 9	17.40	95 6	3.51	4.52
(b) C.W. 16, F	14.15	73.0	14.18	73 3	14 91	77 1	18 05	92 6	3 14	3.90
3. R J. 9, M	13 00	67 4	13 55	70 3	13 68	71 0	17 27	88.9	3.59	4 27
4. D K. 7, M	10 34	70 3		71 0*	10 76	73 1	13 77	92 7	3.01	3.43
5. G.K. 6, M	10 32	59 7	10.98	63 5	10 87	62 9	15 76	90 5	5 86	5 44
6. L.D. 3, M	11 35	63 3	11 73	65.4	11 61	64 7	16.73	92 7	5.12	5.38
Small Patent Ductus Arteriosus										
R.Y. 5, M	10 21	65 1	10.20	65 0	10.41	66 3	15 06	95.3	4.65	4.86

*By oximeter

at catheterization were equivocal, with but a difference of .46 volumes per cent between the mixed caval samples and the pulmonary artery (Table II). The recording of a positive hydrogen curve from the right atrium established the diagnosis of a small atrial septal defect (Figs. 7, *A* and *B*). In addition, the catheter was advanced across the atrial septum.

Table II. *Catheterization data in Patient R. S., 13-year-old boy with small atrial septal defect*

	Content (vol %)	*Saturation (%)*
Inferior vena cava	14 10	78.7
Superior vena cava	12.53	69.9
Right atrium	14.46	79.8
Right ventricle	13 96	77.9
Pulmonary artery	14 04	78 3
Brachial artery	17 12	94.7

Pulmonary arteriovenous oxygen difference: 3.08 vol. %
Systemic arteriovenous oxygen difference: 3.54 vol. %

D. Negative hydrogen curves. In Patient L. S. the clinical findings were a large left-to-right shunt at the ventricular level. However, the presence of left axis deviation on the electrocardiogram raised the possibility of an endocardial cushion defect with both ventricular and atrial septal defects. Oxygen contents at catheterization confirmed the presence of a large ventricular septal defect with no evidence of an atrial septal defect. To definitely rule out an atrial septal defect, hydrogen curves were recorded; these demonstrated the absence of a left-to-right shunt at the atrial level but confirmed the presence of a ventricular septal defect. Thus, this patient is representative of the small group of patients who have ventricular septal defects with left axis deviation.

D. L. was asymptomatic with normal physical findings. He was referred for evaluation because of a prominence in

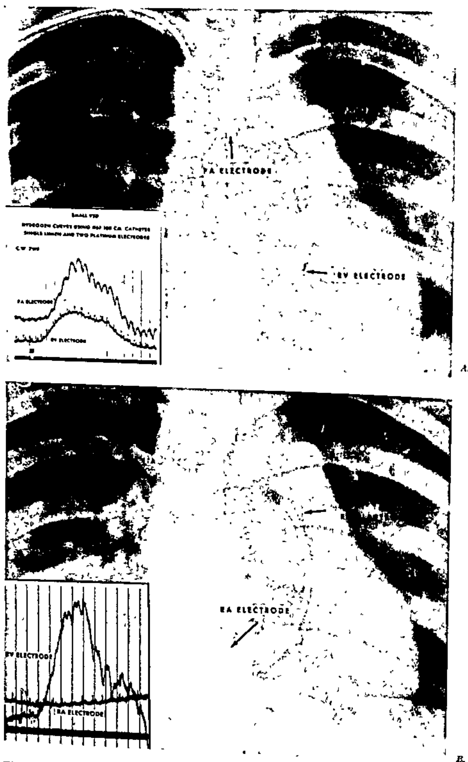


Fig. 4. *A*, Film shows position of catheter electrodes when curves shown in insert were recorded. Early appearance of hydrogen is clearly shown at right ventricular and monary artery electrodes. Note earlier appearance at right ventricular electrode. culation is present on downslope. Inhalation of hydrogen is noted by base-line m Electrodes can be easily seen on film Time lines 1 second apart. *B*, Clearly shows appearance at right ventricular electrode, but not at right atrial electrode, thereb izing shunt at ventricular level.

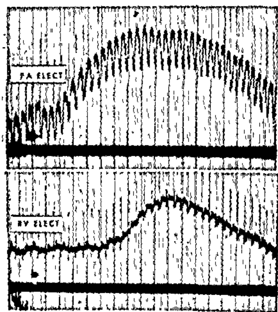


Fig. 5. Small patent ductus arteriosus. Hydrogen curves obtained using a No. 6F 100-cm. catheter with single lumen and one platinum electrode. The marker indicates inhalation of hydrogen. Early appearance of hydrogen is clearly shown by the electrode in the main left pulmonary artery, but not by the electrode in the right ventricle.

the area of the main pulmonary artery which had been noted on a routine chest film. The possibility of mild valvular pulmonary stenosis was doubtful in the absence of an ejection click. The possibility of a small left-to-right shunt could not be excluded. Catheterization revealed normal pressures with no gradient and no evidence of a shunt by oxygen contents. The recording of a negative hydrogen curve from the main pulmonary artery then confirmed the impression of a normal heart.

Discussion

Hyman and associates[9] have noted hydrogen to be more sensitive than either indocyanine green dye or oxygen determinations in detecting experimentally induced left-to-right shunts in dogs. The usefulness and sensitivity of hydrogen curves have also been reported by Jameson and Grayzel,[10] and Frommer and associates.[11] Levy and associates[12] have described a multiple hydrogen-electrode catheter, but no experience in the study of human subjects was contained in their report. That satisfactory hydrogen curves can be recorded on a regular electrocardiographic machine has been shown by Guntheroth.[13]

Nitrous oxide, helium, and krypton[85], as well as the double-catheter dye-dilution technique, have been used to detect and localize small shunts; but they require considerably more time, sampling of blood, and elaborate equipment.[14,15] Also, with krypton[85] and nitrous oxide, the concentrations of the indicator in the venous and arterial samples are compared; consequently, in the presence of a small shunt the ratio may be equivocal. However, with hydrogen, helium, and dye-dilution, the presence of a shunt is established by the definite, early appearance of the indicator, thus leaving no question as to whether a given ratio is significant. Of

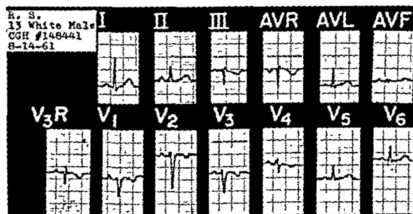


Fig. 6. Electrocardiogram of Patient R. S. The mean QRS vector is about minus 10 degrees.

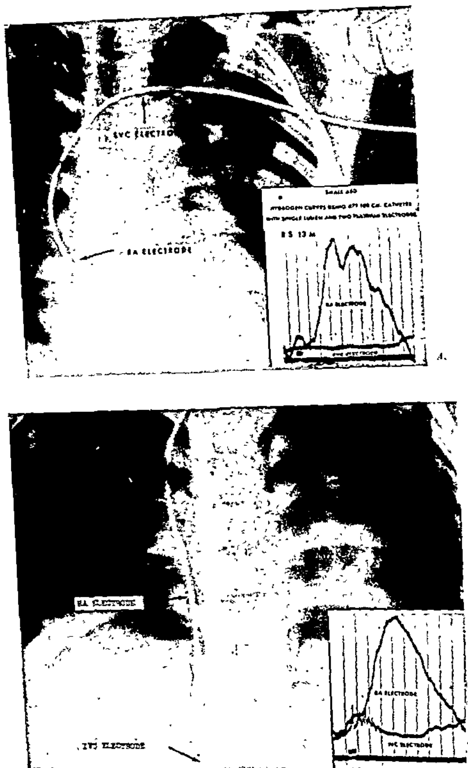


Fig. 7. *A*, Early appearance of hydrogen is clearly shown at right atrial electrode, with negative curve from SVC electrode (innominate vein). *B*, Early appearance of hydrogen is clearly shown at right atrial electrode. Curve from inferior vena cava electrode was negative (although base line shows fluctuations with respiration), thus ruling out an anomalous pulmonary vein at that level. Response of proximal electrode in [illegible] atrium confirms its ability to detect hydrogen.

these three latter indicators, hydrogen is by far the simplest to employ.

The murmur of a small ventricular septal defect may simulate a functional or ejection type of murmur.[16-18] In such cases, it may be impossible to exclude with certainty the presence of a small intracardiac shunt with routine determinations of blood oxygen. Thus, in 33 "normal" children with "functional" murmurs who were catheterized in this laboratory prior to the introduction of the hydrogen technique, the differences in blood oxygen content between right atrium and pulmonary artery ranged from −1.16 to +1.20 volumes per cent. The 8 patients with small shunts reported upon in this communication had variations in blood oxygen content well within this range. Therefore, the possibility exists that if hydrogen curves had been recorded in these "normal" children with functional murmurs, some might have been shown to have a small intracardiac defect.

Recently, Vogelpoel and associates[17] introduced another technique which is intended to identify the small ventricular septal defect clinically. They reported that after the patient inhaled amyl nitrite, the murmur decreased remarkably. However, in Patient C. W. there was no change in the intensity of the murmur with amyl nitrite, even though a small ventricular septal defect was detected with hydrogen (Fig. 4, *A* and *B*).

Other applications of the hydrogen technique include: localization of pulmonary veins which drain anomalously into the caval system, localization of the level of a left-to-right shunt in an uncooperative child in whom the oxygen saturations may be extremely variable, determination whether the postoperative septal defect is definitely closed, and detection of bronchial blood flow.[19] The detection and localization of right-to-left shunts, either in the heart or the lungs, and valvular insufficiency by the use of hydrogenated saline as well as ascorbic acid have been described also.[11,20,21]

More recently, Bargeron and associates[22] described the use of the platinum electrode for direct recording of changes in pO_2 and localization of left-to-right shunts. In addition, ascorbic acid may also be used for the detection and localization of left-to-right shunts, using the platinum electrode.[23] Whether ascorbic acid or direct recording of pO_2 tension is as sensitive as hydrogen has not been established. However, because of their ease of application, hydrogen and ascorbic acid may eventually replace indocyanine dye, both in quantitative and qualitative applications. In fact, Hyman[24] has recently reported a linear system for quantitating hydrogen at a platinum electrode. It is also possible that changes in blood flow may be noted by means of a constant infusion of hydrogenated saline. The use of ascorbic acid for semiquantitation of mitral insufficiency, using two electrodes (one 5 cm. from the tip on a Brockenbrough type of catheter* in the left atrium via transseptal approach,[25] and one in a systemic artery) is presently under investigation in this laboratory.

Summary

In 8 patients with small left-to-right shunts, at either atrial, ventricular, or pulmonary arterial levels, hydrogen curves established the presence of a shunt when serial blood oxygen contents were equivocal.

The extreme sensitivity of the hydrogen technique, as well as its simplicity, low cost, and ease of application in the smallest catheterization laboratory, make it an excellent method for detection and localization of left-to-right shunts.

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Value of examination of carotid pulse by means of resonance electrosphygmographs in relation to intra-arterial pressure tracings

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Cardiographic methods are being used ever more frequently in the diagnosis of atherosclerosis. Many studies have been devoted to the search for the cardiographic criteria of atherosclerosis and to the estimation of their clinical value.[2,3,5-8,11,16,18]

Various types of receivers which press the artery through the skin are used for examination of the pulse.[1,3,6,9,10,12,17-20] However, it has been noticed that tracings made with such receivers are not reproducible.[4] These pressing receivers cause variable distortions in the arteriograms; the distortions depend on the force of compression of the artery, and are very difficult, or even impossible, to eliminate.[5] With the old pneumatic and oil-pneumatic receivers, additional mechanical distortions are caused by air conductibility.[5] As has been shown recently,[6] modern piezoelectric and photoelectric receivers also give distorted arteriograms (Figs. 1 and 2). The clinical diagnostic value of such tracings is doubtful, which is probably the cause of difficulties in a wider application of cardiographic methods. The essential aspect in their development is steady technical progress. Resonance electrosphygmography is a new and remarkable method in this field.[4]

In our clinic, pulse examinations are performed by means of resonance electrosphygmography (Fig. 3), which, after a great number of comparative studies, we have found to be the most suitable.[6-8] The pulse is registered at a distance of about 4 mm., without touching the artery, which eliminates any distorting effects of compression.

Examinations of the carotid artery by means of a resonance receiver were repeated many times in the course of the same experiment in 113 persons.[6,8] The pulse curves obtained from the same artery in the repeated examinations had always very similar, often quite identical, contours. Analysis and evaluation of these curves have shown that electrosphygmographs give reproducible tracings which contain many important details (Figs. 1 and 7).

In 25 examinations the new resonance method has been compared with the piezoelectric one.[6] Table I presents the results of statistical analysis of differences between carotid arteriograms obtained by resonance electrosphygmography and those obtained by piezoelectric receivers. The differences (Figs. 1 and 2) are apparent and statistically significant.

In 34 persons, examinations of the carotid artery by piezoelectric receivers were repeated many times in the course of the same experiment.[5,6] The tracings obtained in repeated examinations had

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always different contours, that is, they were not reproducible. It has been shown that the variable distortions of arteriograms depend on the force of compression of the artery by the piezoelectric receiver (Figs. 1 and 2).

It appears that resonance carotid arteriograms of patients with clinical signs of atherosclerosis of the central arteries show abnormal features which are very characteristic, and which change along with the clinical signs of the disease (Fig. 4).

Table I. Statistical analysis of differences between carotid arteriograms obtained by resonance electrosphygmography and those obtained by piezoelectric receivers (25 comparative investigations)

	Mean*	S.D.	t	p
Upstroke time t (sec.)	0.014	±0.016	4.242	0.01 > p
Ejection time w (sec.)	0.009	±0.014	3.214	0.01 > p
Cardiac cycle time τ (sec.)	0.005	±0.025	0.975	0.4 > p > 0.3
Angle β (degrees)	59.0	±39.4	7.468	0.01 > p
Elasticity index e	1.0	±0.77	6.410	0.01 > p
Dicrotic index d (%)	65.0	±42.1	7.720	0.01 > p

*Mean difference of the respective dimensions. The differences are statistically significant.

Table II. Statistical analysis of differences between carotid arteriograms obtained by resonance electrosphygmography in 69 patients with atherosclerosis and those obtained in 44 healthy persons

	Patients		Controls		t	p
	Mean	S.D.	Mean	S.D.		
Upstroke time t (sec.)	0.05	±0.009	0.10	±0.016	2.777	0.01 > p
Angle β (degrees)	149.7	±21.0	51.7	±23.9	3.101	0.01 > p
Elasticity index e	0.63	±0.15	1.4	±0.28	2.295	0.05 > p > 0.02
Dicrotic index d (%)	122.9	±40.6	42.8	±18.0	1.817	0.1 > p > 0.05
Plateau time p (sec.)	0.18	±0.023	0.16	±0.026	0.581	0.6 > p > 0.5
Mean arterial pressure (mm Hg)	101.6	±11.8	91.6	±10.4	0.659	0.6 > p > 0.5
Cardiac cycle time τ (sec.)	0.92	±0.14	0.85	±0.12	0.388	0.7 > p > 0.6

Some of the indices (time t, angle β, index e) show statistically significant differences. According to Chlebus.[8]

Table III. Results of statistical analysis of dimensions of resonance carotid arteriograms and intracarotid pressure tracings obtained in 19 comparative investigations

	Mean*	S.D.	t	p
Upstroke time t (sec.)	0.0034	±0.0092	1.590	0.2 > p > 0.1
Plateau time p (sec.)	0.001	±0.010	0.420	0.7 > p > 0.6
Ejection time w (sec.)	0.005	±0.021	1.016	0.4 > p > 0.3
Angle β (degrees)	1.9	±4.4	1.835	0.1 > p > 0.05
Elasticity index e	0.004	±0.090	0.187	0.9 > p > 0.8
Dicrotic index d (%)	0.4	±9.2	0.184	0.9 > p > 0.8

*Mean difference of the respective dimensions.
The indices do not show statistical differences, and the contours of the compared curves can be considered to be in accordance with each other.

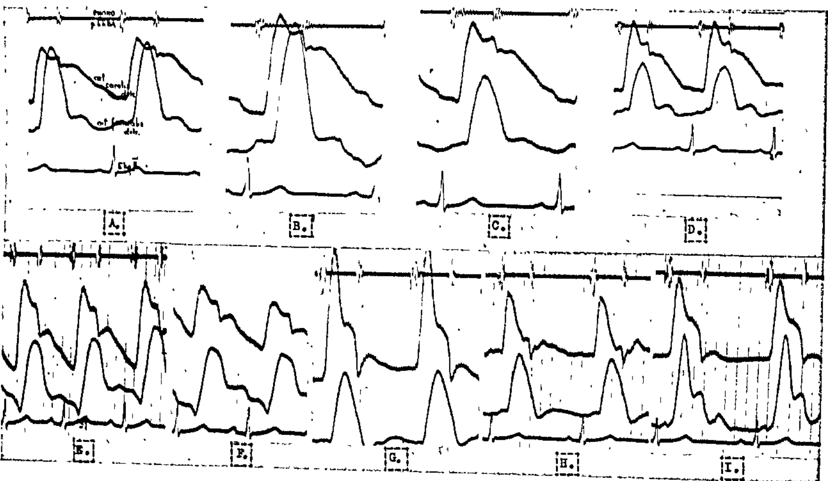


Fig. *1*. The same order of curves is preserved in all sections. *From top to bottom:* Phonocardiogram, carotid arteriogram, femoral arteriogram (in *I*, a radial instead of a femoral arteriogram is presented), and ECG Lead II. *A-D*, Polycardiograms of a 26-year-old healthy male. The carotid arteriograms obtained from the same artery in four repeated examinations in the course of the same experiment by means of a resonance receiver have very similar, often nearly identical contours, i.e, are reproducible. These are normal contours, characteristic of healthy people. Compare with Fig. 4. *E-I*, Polycardiograms of a 16-year-old healthy female. The carotid arteriograms registered with a resonance receiver in two examinations in the course of the same experiment have normal and very similar contours (*E* and *F*). The next three carotid arteriograms (*G*, *H*, and *I*), which were obtained in the same patient with a piezoelectric receiver in three examinations in the course of the same experiment, differ from the resonance curves and from each other. They are distorted in varying degrees, i.e., are not reproducible.

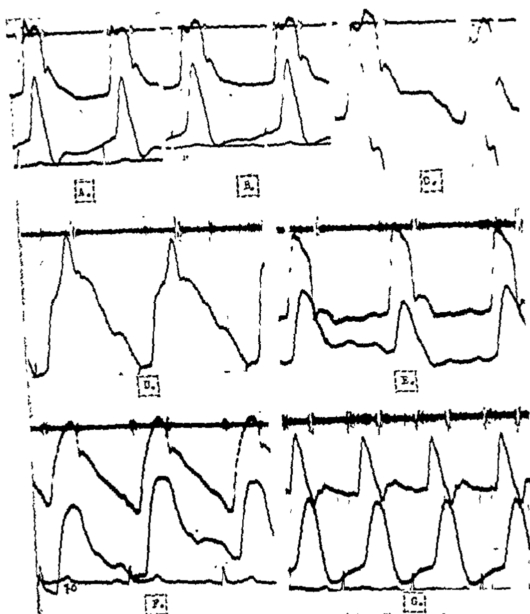
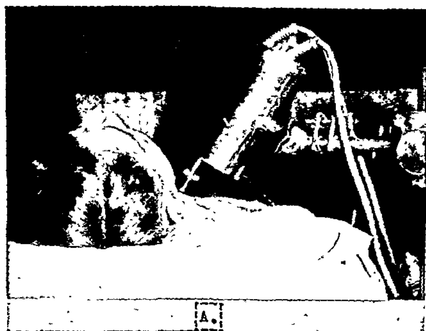


Fig. 2. The same order of curves is preserved in all sections *From top to bottom* Phonocardiogram, carotid arteriogram, femoral arteriogram (in *C*, a radial instead of a femoral arteriogram is presented), and ECG Lead II. *A-C*, Polycardiograms of a 54-year-old patient with coronary heart disease. All three carotid arteriograms have been registered in the course of the same experiment in three repeated examinations of the same artery—by means of a piezoelectric receiver. The tracings are not reproducible; their contours vary greatly—from quite normal (*A*) to clearly pathologic (*C*). Compare with Fig 4. *D*, *E*, Carotid arteriograms of a 65-year-old man with coronary heart disease. The curve obtained with a resonance receiver shows a contour typical of atherosclerosis (*D*). A piezoelectric receiver gives an artificially normal tracing (*E*). Compare with Fig. 4. *F*, Arteriogram registered with a photoelectric receiver in a 58-year-old man with generalized atherosclerosis. It is clearly distorted Compression of the artery eliminates certain important details of the curve, particularly the junction between the ascending limb and plateau The curve is artificially rounded. *G*, An exceptionally distorted carotid arteriogram of a 30-year-old patient with coronary heart disease taken with a piezoelectric receiver. The artery was pressed considerably.



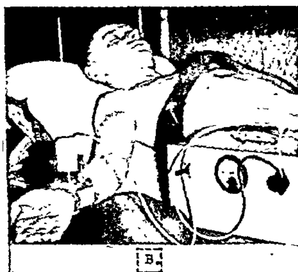




Fig. 3. Two prototypes of resonance electro-phygmographs during examination of the arteries. The receivers are not pressing on the vessels. The distance from the skin is about 4 mm. The examinations presented in this paper have been performed by means of model I (*A*). Model II (*B* and *C*) is an improvement in this field. The support of this model must be built and set in such a way that it does not press on the artery. This is easy to accomplish because of the light weight of the receiver.

Statistical analysis (Table II) permits consideration of these changes in contour (see Fig. 7: upstroke time *t*, angle *β*, elasticity index *e*) of the resonance carotid arteriogram as a diagnostic criterion.[8] These data, substantiated from clinical inference, call for further studies with pathologic confirmation.

The investigations suggest that the resonance method, only recently introduced into pathophysiologic research by D. Cembala,[4] is better than previously used methods. It seems to be of theoretical and practical interest.

The objection has also been raised that resonance receivers, by taking the arterial wall oscillations at a distance, register changes in volume, which are probably influenced by the elastic resistance of the surrounding tissues.[4,6]

Because of the difficulties in the early diagnosis of atherosclerosis and the clinical needs in this field,[2,11] further investigation has been carried out in order to determine the value of this new method. The present work is an attempt to show to what extent resonance electrosphygmographs reproduce the intra-arterial pressure oscillations of the carotid artery.

Methods and results

Comparative examinations have been made of patients from the Neurosurgical Clinic. They had to undergo diagnostic cerebral angiography, with a contrast medium being injected into the carotid artery. Half an hour after the premedication, which consisted of Dolantin, Largactil, and Phenergan, carotid arteriograms were registered by means of a resonance electrosphygmograph (Fig. 3) on a modern polycardiograph.[4,6] For comparison, in several cases, tracings were also made by means of photoelectric and piezoelectric pressing receivers. The carotid artery was then punctured at the same point with a needle which was 1 mm. in diameter, and intra-arterial pressure tracings were registered by an electromanometer. Special care was taken so that both recordings would follow each other closely. Then cerebral x-ray angiography was performed.

The arteriograms taken with resonance receivers were registered on a modern mirror-galvanometer polycardiograph manufactured by the George Petit Company. The intra-arterial pressure curves were obtained by an electromanometer manufactured by the Beaudouin Company. The principles of the construction and operation of the resonance electrosphygmographs have been described in detail elsewhere.[4,6] Dr. D. Cembala, of Crakow, Poland, is the author of this method.[4]

Nineteen comparative examinations were made. The carotid arteriograms obtained with resonance receivers are very similar in shape to, or even identical with, the intra-arterial pressure curves (Figs. 5 and 6). This conformity occurs in all arteriograms, both normal and pathologic ones. Certain minor differences may depend on the different speeds at which the paper moves through the respective recording machines (Fig. 6). At greater speeds the curve becomes somewhat drawn out, and sharp peaks become more rounded. This especially concerns the angle β. It was very difficult to avoid this and obtain the same speed of paper movement in both machines.

On the other hand, carotid arteriograms taken with piezoelectric and photoelectric receivers differ greatly from the pressure curves taken inside the artery (Fig. 6). The compression of the arterial wall by the receiver distorts the arteriogram, lowering its plateau, its dicrotic notch, and dicrotic wave, thus completely changing the character of the curve. The results of this examination confirm the previous observations[4] (Figs. 1 and 2; Table I).

Curves obtained by both methods have been carefully analyzed geometrically. The following dimensions characterizing the shape of the central pulse curves were taken into consideration (Fig. 7): (1) upstroke time t (sec.); (2) duration of systolic plateau p (sec.); (3) ejection time w (sec.); (4) angle between ascending limb and plateau β (degrees); (5) elasticity index e ratio: distance a/distance b; (6) dicrotic index d (%) ratio: distance c distance a.

These are the essential elements of the central pulse curve often used in diagnostics.[5,6,8,9,15,18] Some of them (time t, angle β, index e) characterize arterial elasticity and can be used to diagnose atherosclerosis.[8,9] Ejection time w characterizes the dynamics of systole of the left ventricle of the heart.[1,3,6,7] Index d is considered to be characteristic of pe-

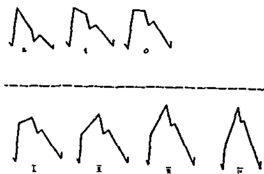


Fig. 4. Diagram which shows the different patterns of carotid arteriograms obtained with resonance receivers in healthy persons (*top*) and in patients with coronary disease (*bottom*). Accord[illegible] bus.[4]

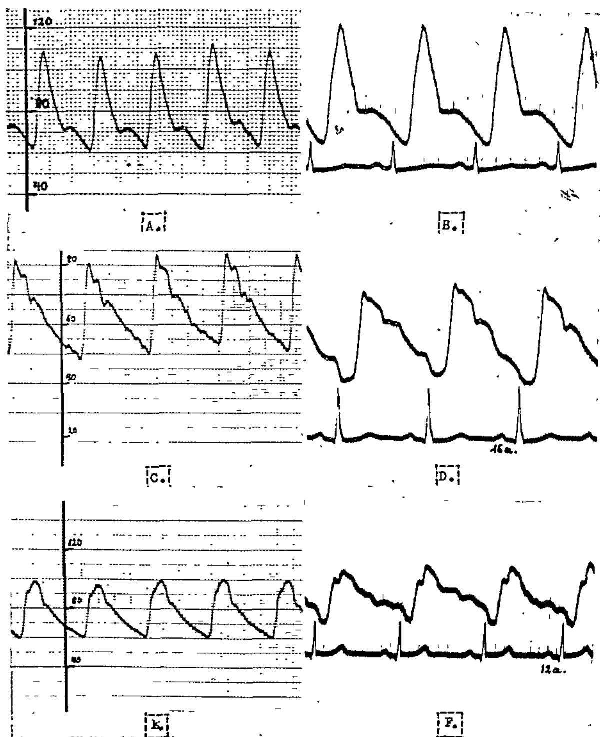


Fig. 5. Comparison of pressure curves registered inside the carotid artery (*A,C,E*) and carotid arteriograms obtained with resonance receivers (*B,D,F*) in 3 subjects shows that their contours are similar, and almost identical. The pressure curve (*A*) and resonance arteriogram (*B*) of the carotid artery taken from a 22-year-old woman show nearly identical contours. According to the results of the previous investigation, they are typical of young people with unimpaired elasticity of the arterial system. *C* and *D*, Intracarotid pressure curve and resonance carotid arteriogram, respectively, of a 50-year-old man; the contours are very similar and typical of healthy adult people. *E* and *F*, Analogical comparison of curves of a 62-year-old man; the contour is typical of arterial atherosclerosis. Compare with Fig. 4.

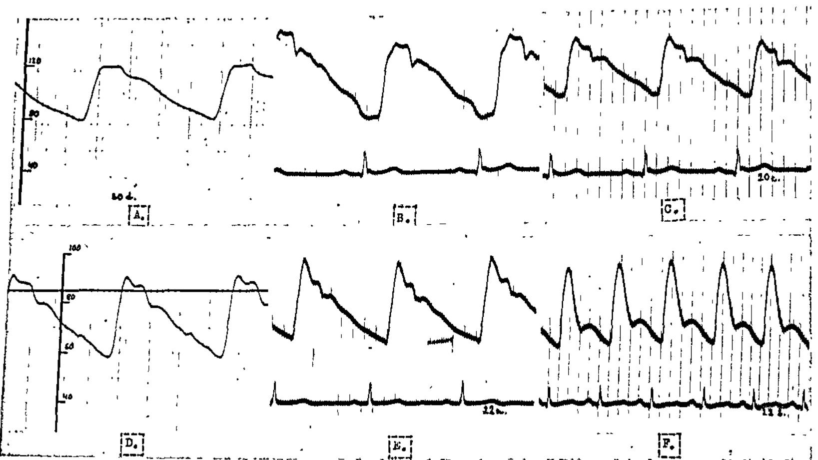


Fig. 6. *A, B, C,* Tracings obtained from a 24-year-old man. *A,* Intra-arterial pressure curve of the carotid artery. *B,* Carotid arteriogram obtained with a resonance receiver. The contour is very similar to the intra-arterial pressure curve. Minute differences arise from the different rates of speed of the paper in the machines. *C,* Carotid arteriogram registered with a photoelectric receiver. It is clearly distorted in comparison with the intra-arterial pressure tracing. The pressure exerted on the artery by the receiver lowers the plateau of the pulse curve and essentially deforms the whole descending limb. *D, E, F,* An analogical comparison of tracings obtained from a 30-year-old woman. Intracarotid pressure curve (*D*) and carotid arteriogram obtained with a resonance receiver (*E*) show very similar contours. Minor differences arise from the different speeds of the paper in the machines. A carotid arteriogram registered with a piezoelectric receiver (*F*) is clearly distorted in relation to the intra-arterial pressure curve. Compression of the artery by the piezoelectric receiver clearly lowers the plateau and the dicrotic notch, and thus completely changes the character of the curve.

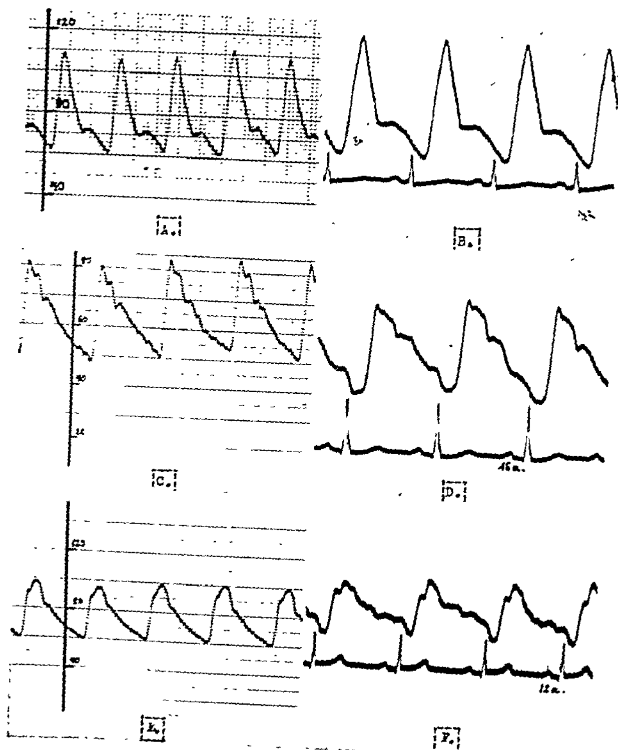


Fig. 5. Comparison of pressure curves registered inside the carotid artery (*A,C,E*) and carotid arteriograms obtained with resonance receivers (*B,D,F*) in 3 subjects shows that their contours are similar, and almost identical. The pressure curve (*A*) and resonance arteriogram (*B*) of the carotid artery taken from a 22-year-old woman show nearly identical contours. According to the results of the previous investigation, they are typical of young people with unimpaired elasticity of the arterial system. *C* and *D*, Intracarotid pressure curve and resonance carotid arteriogram, respectively, of a 50-year-old man; the contours are very similar and typical of healthy adult people. *E* and *F*, Analogical comparison of curves of a 62-year-old man; the contour is typical of arterial atherosclerosis. Compare with Fig. 4.

tain all the essential details which are particularly useful for evaluation of arterial elasticity.

5. The conformity of intra-arterial pressure tracings and arteriograms obtained by means of electrosphygmographs at a distance, without pressing the artery, is also of theoretical interest, and deserves further analysis.

Summary

As has been shown before, the contour of the resonance carotid arteriogram may serve as a diagnostic criterion of arterial atherosclerosis. The arteriograms were registered by means of resonance electrosphygmographs at a distance, without pressing the artery. This study was an attempt to ascertain to what degree resonance receivers reproduce the intra-arterial pressure oscillations. In 19 experiments, carotid arteriograms were taken with resonance receivers, and intra-arterial pressure curves were registered by means of an electromanometer. The contours of the curves obtained by both methods are very similar, often quite identical. Measurements and statistical comparisons of the essential elements of these curves do not show significant differences. Arteriograms registered with piezoelectric and photoelectric pressing receivers differ essentially from the intra-arterial pressure curves. The distortions are variable and increase along with the force of external pressure exerted on the artery. For this reason the diagnostic value of widely used piezoarteriograms gives rise to serious objections.

These comparisons provide additional evidence in favor of the resonance method, which is very useful in examination of the carotid pulse, particularly for the evaluation of arterial elasticity. Resonance receivers enable us to eliminate the distorting effect of external pressure on the artery, so that tracings thus recorded reflect accurately the intra-arterial pressure oscillations.

The examinations were carried out partly in the Circulatory Center of the Radiology Department (Head: Prof. W. Zawadowski, M.D.) on patients from the Neurosurgical Clinic (Head: Prof. J. Choróbski, M.D.) of the Warsaw Medical Academy. I wish to acknowledge the kind aid extended to me by the workers of these departments by letting me perform my experiments.

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Thirteen-year survival with acquired interventricular septal defect after myocardial infarction

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In a previous communication,[1] we reported 3 personally observed cases of perforation of the interventricular septum incident to myocardial infarction, in which the diagnosis had been made before death. One of the patients (Case 3) of that report was still living at the time of publication, March, 1954, and it was our opinion that she had survived longer than any patient previously reported with this disorder. This patient has since expired at the age of 88 years, on June 19, 1960, 13 years and 4 months after her myocardial infarction and septal perforation. Autopsy confirmed the clinical diagnosis of acquired interventricular septal perforation and revealed that death was hastened by an unrelated disease, which was also suspected before death.

Case report

A 75-year-old white woman, previously free of known cardiovascular disease, collapsed with severe retrosternal pain and dyspnea on Feb. 20, 1947. She was seen by one of us (J.C.S.) at her hotel several hours after the attack began and was found to be in mild shock. Cardiac auscultation was normal; no murmurs were audible.

Treatment for acute myocardial infarction, which consisted of an oxygen tent, morphine sulfate for pain, and nursing care, was provided in the patient's hotel room during the course of this illness. On February 21, a Grade 5, harsh, pansystolic murmur was first heard over the entire chest, loudest at the fourth and fifth left intercostal spaces parasternally, where a systolic thrill was easily palpable. An electrocardiogram taken on the third day of her illness revealed deep QS waves in Leads I, II, and CF_4 (Fig. 1,*a*). Subsequent tracings confirmed the presence of extensive infarction which involved simultaneously the anteroseptal and posterior myocardium, a pattern previously described by Roesler and Dressler as indicating septal infarction.[2]

Soon after the murmur and thrill were noted, the patient developed venous distention, edema, ascites, and hepatomegaly. She remained in a state of chronic right ventricular heart failure with persistence of the murmur and thrill for the rest of her life. Basilar râles, orthopnea, and other evidence of left ventricular failure were present during her last 5 years. Electrocardiograms taken serially in succeeding years showed increasing right axis deviation (Fig 1,*b*, *c*, and *d*). Management consisted of a low-sodium diet, various diuretics, and Gitaligin The Gitaligin was given from 1955 until her death. Weekly injections of mercurials were given, at first in combination with ammonium chloride, and later with daily chlorothiazide.

Except for several months in 1957, when she was put at strict bed rest because of stasis ulcer of her leg after a dog bite, she remained ambulatory until the fall of 1959 At that time she developed a moderate hypochromic anemia, and the stool tests were persistently positive for occult blood. Hemoglobin was 7.6 Gm , and erythrocytes 2.85 million. She refused to undergo gastrointestinal x-ray examination. Her blood picture improved modestly on iron therapy. The remaining months of her life were dominated by gradual failure of nutrition, signs of obstruction in the lower intestine, and increasing heart failure. She died, according to her wishes, in her hotel suite on June 19, 1960, at the age of 88 years.

Autopsy findings.

CARDIOVASCULAR SYSTEM (GROSS). "The pericardium is adherent to the apex of the left ventricle by fibrous tissue and contains a small amount of fluid. The heart weighs 510 grams. On opening the heart in the direction of blood flow an aneurysm

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The electrocardiogram in certain anomalies of the coronary arteries

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Congenital anomalies of the coronary arteries occur infrequently. Because of the relatively few patients with such anomalies, and because any one physician sees so few patients with this anomaly, the electrocardiographic patterns in patients with anomalous coronary arteries have not been carefully described. The purpose of this paper is to describe the electrocardiographic findings in selected types of anomalous coronary arteries as determined from a study of the reports in the medical literature.

Anomalous left coronary artery arising from the pulmonary artery. Of the various anomalies of the coronary arteries, the electrocardiogram has been most adequately described for anomalous origin of the left coronary artery from the pulmonary artery.[1] The clinical and electrocardiographic findings in this anomaly are so characteristic that it is possible to make the diagnosis during life in the large majority of patients.[2] The usual clinical picture is that of an infant who, after appearing normal for the first 2 or 3 months of life, develops clinical signs of angina pectoris. The episodes of angina pectoris usually occur while the infant is feeding or soon thereafter. During the anginal attack the infant may scream as if terrified, sweat profusely, and become dyspneic and cyanotic. The roentgenogram shows an enlarged heart with a dilated left ventricle. Significant cardiac murmurs are usually not audible. However, a to-and-fro murmur similar to that heard in patent ductus arteriosus may be present. This is due to an arteriovenous shunt of blood from the right coronary artery, which originates from the aorta, into the anomalous left coronary artery, which drains into the pulmonary artery.[3,4] Several instances of an anomalous origin of the coronary artery from the pulmonary artery in association with mitral insufficiency have been reported in adults.

The electrocardiogram in cases of anomalous left coronary artery arising from the pulmonary artery has been described by several investigators.[1,5,6] The characteristic electrocardiographic findings (Figs. 1 and 2) are as follows: The mean electrical axis of the QRS complex lies between 60 and 90 degrees in the frontal plane. Relatively deep and wide Q waves ("coronary" type of Q waves) are present in Leads I, aV_L, V_4, V_5, and V_6. A tall R wave is present in Lead V_4 and a deep S wave is present in Lead V_1. The T wave is almost invariably inverted in Lead I and is frequently inverted in Lead II. T-wave inversion is also frequent in Leads V_5 and V_6. The S-T seg-

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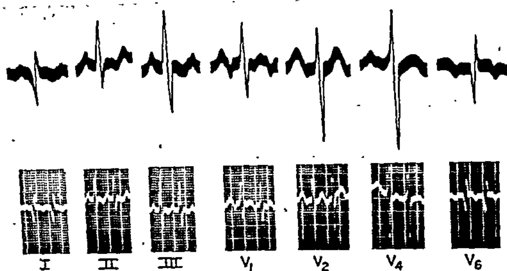


Fig. 1. Typical electrocardiogram from a patient (2 months old) with anomalous origin of the left coronary artery from the pulmonary artery.

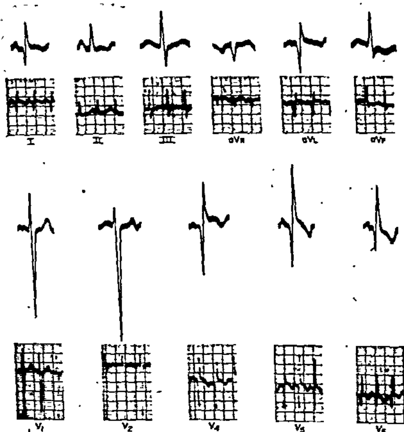


Fig. 2. Typical electrocardiogram from a 5-week-old patient with anomalous origin of the left coronary artery from the pulmonary artery. (Reprinted courtesy British Medical Journal Publishing Department. From Keith, J. D.: Brit. Heart J. 21:149, 1959.)

ment may be elevated or depressed in Leads I, V_5, and V_6. Abnormalities in conduction are infrequent.

The electrocardiogram recorded during episodes of angina pectoris, as for example during the pain associated with feeding, may demonstrate S-T-segment and T-wave changes consistent with myocardial ischemia. These changes are the same as the well-known changes seen in adults during episodes of angina pectoris.

Approximately 17 per cent of the patients who have the left coronary artery arising from the pulmonary artery survive into adult life. The electrocardiograms of adult patients with this syndrome show deep, wide S waves in Leads II and III (Fig. 3) and in Leads V_1 through V_3 or V_4. Prominent R waves are present in Leads V_5 and V_6 or only in Lead V_6. The changes are similar in many respects to those seen in apical myocardial infarction.[7]

COMMENT. Deep Q waves in Leads I, V_5, and V_6 in association with S-T-segment alterations and T-wave inversion in the electrocardiogram of an infant who was apparently normal during the first few months of life should suggest the diagnosis of anomalous origin of the left coronary artery from the pulmonary artery. Confirmation of attacks of angina pectoris may sometimes be obtained by feeding the infant and observing the electrocardiogram for signs of S-T-segment depression during any episodes of distress that may develop.

The presence of deep S waves in Leads II, III, V_1, V_2, and V_3 is consistent with localized hypertrophy of the posterobasal portion of the left ventricle. Recently, we have described[7-10] the necropsy and electrocardiographic findings in patients with apical myocardial infarction as well as in patients with extensive loss of left ventricular musculature due to advanced arteriosclerotic disease of the left coronary artery, and in whom the right coronary artery was found to be patent at necropsy. In these patients the posterobasal portion of the left ventricle was greatly hypertrophied because of an adequate collateral blood supply from the relatively healthy right coronary artery, whereas the anterolateral portion of the left ventricle was thin and fibrotic. Aneurysmal dilatation of the apex of the left ventricle was frequently observed.

The electrocardiogram displayed deep S waves in Leads II, III, V_1, V_2, and V_3. A tall R wave was usually present in Lead V_6. However, if the circumflex branch of the left coronary artery was patent, the R wave was also usually tall in Lead V_5, and, at autopsy, localized posterobasolateral hypertrophy was present. It was postulated that the forces developed during depolarization of the area of localized hypertrophy were large, whereas those developed during depolarization of the fibrotic anteroseptal and lateral portions of the left ventricle were small. Thus, the resultant major cardiac vectors were directed superiorly, to the left, and posteriorly and were thought to be responsible for the deep, wide S waves found in the electrocardiogram. The earlier vectors produced during depolarization in the region of the thin fibrotic anterolateral portions of the left ventricle resulted in the relatively small R waves which were seen in Leads II, III, V_3, V_4, and V_5 or V_3 and V_4. The late mean instantaneous vectors of the QRSsÊ loop of these patients in which the tetrahedral system of electrode placement was used were directed superiorly, to the left, and posteriorly. The QRSsÊ loops were inscribed with a counterclockwise rotation. The early vectors, directed inferiorly, to the right, and then to the left, were remarkably shortened.[10]

Necropsy studies of patients with anomalous origin of the left coronary artery from the pulmonary artery have shown that the left ventricle is hypertrophied and dilated. However, the portion of the myocardium supplied by the left coronary artery is fibrotic, the trabeculae carneae are flattened, and atrophy of the anterior papillary muscle is frequent. The apex of the heart may be "infarcted," and in many instances is aneurysmally dilated. On the other hand, the posterobasal portion of the left ventricle is relatively normal or hypertrophied, since it is nourished by the normal right coronary artery.[11-14] The extensive loss of muscle tissue throughout the left ventricle, and the normal or hypertrophied muscle present in the posterobasal portion of the left ventricle found in patients with anomalous left coronary artery is identical to that found in patients with severe occlusive arteriosclerotic disease of the left coronary artery and healthy right coronary arter-

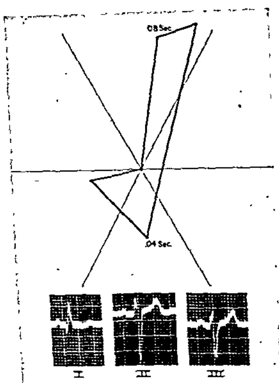


Fig. 3. Unipolar limb leads and constructed frontal plane QRS loop in an adult patient with anomalous left coronary artery. The deep S waves in Leads II and III are consistent with localized posterobasal myocardial hypertrophy. Consult text for details. (From Gouley, B. A: Am. Heart J. 40:630, 1950.)

ies.[8-10] The electrocardiograms from both groups of patients are also remarkably similar. The S_2S_3 pattern is especially well developed in patients with anomalous left coronary artery who survive to adulthood. This is probably due to the more extensive compensatory localized hypertrophy which develops with time.

Anomalous right coronary artery arising from the pulmonary artery. Only 5 patients with an anomalous right coronary artery arising from the pulmonary artery have been described.[15-19] The electrocardiogram shown in Fig. 4 was sent to us by Doctor R. H. Pribble, and is, in so far as we know, the only electrocardiogram ever published for a patient with an anomalous right coronary artery arising from the pulmonary artery. This patient also had a history of rheumatic carditis. However, only minimal mitral stenosis was found at necropsy. Angina pectoris was a prominent feature of the patient's clinical history. Yet, at postmortem examination there was only slight coronary atherosclerosis. The electrocardiogram does not show any characteristics which would make one suspect an anomalous origin of the right coronary artery. Life expectancy is probably normal in persons with an anomalous right coronary artery arising from the pulmonary artery.

Single coronary artery. Single coronary artery is an infrequent but by no means rare anomaly of the coronary circulation. The single coronary artery may arise from any of the aortic sinuses and follow the course of one or both coronary arteries, or else may follow a completely atypical course.[20] Life expectancy is probably not normal for those who have this anomaly, but almost all patients survive to adulthood.

Although few electrocardiograms of patients with single coronary artery have been published, these are of considerable interest. Roberts and Loube[21] and Tremouroux and associates[22] have described patients with this defect in whom the electrocardiogram showed infarction of the right atrium and right ventricle. In Roberts and Loube's patient, the electrocardiogram showed an idioventricular rhythm with a rapidly changing atrial mechanism. The S-T segment in Lead I was greatly depressed. It was elevated in Leads II and III, and Q waves were present in Leads II and III. The S wave in Lead CF_1 was notched. The $P\text{-}T_a$ segment was elevated in Lead II (Fig. 5). The electrocardiogram from the patient reported on by Tremouroux and associates was remarkably similar; it showed atrial fibrillation, idioventricular rhythm, and abnormalities of the $P\text{-}T_a$ segment. Necropsy studies in both patients demonstrated occlusion of the branch of the single coronary artery which followed the distribution of the right coronary artery.

COMMENT. Relatively few reports of atrial infarction diagnosed during life have been published. Yet, 2 cases associated with the relatively infrequent congenital defect of a single coronary artery have been described. Although it cannot be said that the presence of a single coronary artery can be diagnosed electrocardiographically, the presence of right ventricular and right atrial myocardial infarction may provide some clue

Fig. 4. Electrocardiogram from a 55-year-old woman whose right coronary artery originated from the pulmonary artery. (Courtesy of Dr. R. H. Pribble.)

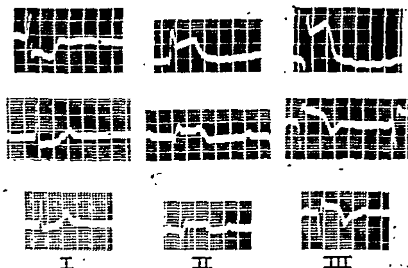


Fig. 5. Serial electrocardiograms from a patient with a single (right) coronary artery. Note development of Q_2-Q_3 pattern and elevation of S-T_2 segment in Lead II of tracing on the right. (From Roberts, J. T., and Loube, S. D.: Am. Heart J. 34:188, 1947.)

to the antemortem diagnosis of this anomaly.

Summary

The electrocardiogram in selected congenital anomalies of the coronary circulation has been reviewed. The electrocardiographic characteristics of anomalous left coronary artery arising from the pulmonary artery are fairly diagnostic. Furthermore, correlation of the electrocardiogram with the necropsy findings in this defect lends further support to the concept of localized myocardial hypertrophy previously presented from this laboratory.

The electrocardiogram of patients with single coronary artery was not considered to be diagnostic. However, the diagnostic possibilities of electrocardiographic signs of right atrial and right ventricular myocardial infarction were mentioned.

It is remarkable how many detailed studies of the heart and coronary circulation of patients with anomalous coronary arteries have been published in which no electrocardiograms have been reported. More extensive electrocardiographic studies in patients with anomalies of the coronary circulation are needed if the accuracy of antemortem diagnosis is to be improved.

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The systemic and coronary hemodynamic effects of arteriovenous fistulas

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Many hemodynamic studies of arteriovenous fistulas have been made in the past, and the ancient[1] and more recent[2] history concerning them has been reviewed; therefore, no attempt will be made here to review the literature other than as it applies directly to the present study. Of particular interest, however, are the group of experimental studies concerning the readjustments which occur in systemic and regional blood flows when arteriovenous fistulas are opened or closed, since these interrelationships are closely related to the readjustments in coronary circulation under the same circumstances. Information on coronary blood flow seems to have been derived only from open-chest preparations,[3-6] and frequently in subjects with such extensive surgical procedures that the control state was far from physiological. Hence, the problem has been restudied, utilizing the nitrous-oxide method, in the hope of deriving information more closely related to a clinical situation.

Material and methods

Hemodynamic studies are reported here on two series of dogs which had an average weight of 19.3 kilograms (range 13.2-26.8 kilograms). In the first series, an arteriovenous fistula approximately 1 cm. in length was created surgically between the femoral artery and vein. Most of the animals had considerable swelling and edema of the extremity for a period of time after the operation was performed, but they were permitted to recover for several weeks, so that at the time of study their general condition seemed good, and their state of cardiac function as measured hemodynamically was satisfactory. At the time of study a large clamp padded with foam rubber was placed in the optimal position for the fistula to be closed by external compression. The studies were alternated, so that in one half of the observations the first study was made with the arteriovenous fistula closed, and in the other half the first study was made with the fistula open. Thus, data were randomized so as to minimize the effects of anesthesia, manipulation, and loss of blood. In each case, sufficient time, approximately 20 minutes, was allowed for the hemodynamic effects of the change to become stable after the fistula was opened or closed. The cardiac output and coronary flow, therefore, were determined during

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the period from 20 to 35 minutes after the change of state.

Although the chronic arteriovenous fistulas seemed to be quite significant hemodynamically when they were made, it was apparent from the response to their opening and closing that the amount of flow through the fistula was insufficient to give a clear picture as related to coronary hemodynamics. Therefore, in the second series of animals a group (Group II of the present data) was studied with an acute, large fistula between the abdominal aorta and vena cava. The plan of study was the same in this group except that the aortocaval fistula was created by inserting a large-bore T-tube in the aorta and another in the vena cava. The fistula was opened and closed by a clamp on the plastic tubing which connected the two T-tubes. The animals with the aortocaval fistula were given heparin in order to prevent clotting. As in the case of the chronic fistulas, the studies were randomized in the same manner.

In the subjects with chronic fistulas, anesthesia was secured by administration of 3 mg. per kilogram of morphine sulfate subcutaneously, followed in 1 hour by intravenous administration of 0.25 ml. per kilogram of a 50/50 mixture of Dial-urethane and veterinary pentobarbital.* During the ensuing hour, after the administration of the anesthetic, cardiac catheters were manipulated fluoroscopically into the pulmonary artery, coronary sinus, and right atrium. Two Cournand needles were placed percutaneously in the femoral artery opposite the site of the arteriovenous fistula. One hour after the anesthetic was given the first cardiac output was determined by the Fick principle, with collection of expired air for a 5-minute period in a Tissot spirometer, and coronary blood flow was determined by the nitrous-oxide saturation method. Cardiac output was also determined by the Hamilton indicator-dilution method during the determination of cardiac output by the Fick principle and again during the measurement of coronary blood flow by using indocyanine green as the indicator and a Gilford model 103-IR densitometer attached to a Gilson macropolygraph for recording indicator-dilution curves. Blood for the indicator-dilution curves was withdrawn into a constant-withdrawal syringe* and infused again immediately after each dye curve. Calibration was made with blood withdrawn after the end of the study. In the animals in which the fistula was created acutely the anesthetic was the same, but was given prior to the surgical procedure, and the hemodynamic study was performed as soon as the preparation was completed and stable. Determination of cardiac output with the indicator-dilution method was not made in those animals with the large fistulas, since recirculation occurred too early for a satisfactory exponential downslope to be obtained.

Pressure in the right atrium and pulmonary and systemic arterial pressures were recorded at appropriate intervals with Statham strain gauges on the Gilson macropolygraph. The mean pressure was determined by electrical integration of the pressure curve. Cardiac rate was determined from an electrocardiographic lead. The oxygen and carbon-dioxide content of the blood was determined by the Van Slyke-Neill method, whereas analyses for nitrous oxide were made by the method of Orcutt and Waters. The oxygen and carbon-dioxide content of expired air was determined by the method of Scholander. Whole blood pH was determined with a Cambridge model R pH-meter. Formulas used for calculation of cardiac output, cardiac work, and cardiac efficiency are those generally used.[6] The work was calculated as cardiac output multiplied by mean blood pressure in the femoral or pulmonary artery and converted to kilogram-meters per minute by appropriate constants. Statistical testing was done by the t-test, and correlation coefficients were calculated by standard formulas.

Results

As is expected when an arteriovenous fistula is opened, there was a sudden de-

*The Dial-urethane was furnished by Ciba Pharmaceutical Products, Inc., Summit, N.J., and contains 100 mg. of Dial, 400 mg. of monoethylurea, and 400 mg of urethane per milliliter. Veterinary pentobarbital contains 60 mg. per milliliter of pentobarbital.

*Harvard Apparatus Company, Inc. [illegible]

Table I. Hemodynamic effects of femoral A-V fistula

Parameter	*Fistula closed*	*Fistula open*	*% Change*	*Standard error of the mean*	*p Value <*
Heart rate (beats/min.)	87	103	+18.4	6.138	0.02
Mean arterial blood pressure (mm. Hg)	117	99	−15.4	3.175	0.001
Mean pulmonary arterial blood pressure (mm. Hg)	14	16	+14.3	0.963	0.4
Mean right atrial blood pressure (mm. Hg)	4.1	4.3	+4.9	0.348	0.6
Oxygen consumption (c.c./min.)	102	101	−1.0	2.387	0.7
Body respiratory quotient	0.79	0.77	−2.5	0.029	0.8
Arteriovenous oxygen difference (ml./100 ml. of blood)	3.5	2.7	−22.9	0.269	0.02
Coronary sinus oxygen content (ml./100 ml. of blood)	5.0	4.7	−6.0	0.419	0.5
Arterial-coronary sinus O_2 difference (ml./100 ml. of blood)	10.9	11.8	+8.3	0.500	0.2
Cardiac respiratory quotient	1.02	0.88	−13.7	0.065	0.1
Arterial hematocrit (%)	41	41	—	—	—
Cardiac output (L./min.)	3.1	4.1	+32.3	0.352	0.02
Total peripheral resistance (c.g.s. units)	*3,180*	*2,116*	*−33.5*	*245.5*	*0.01*
Total pulmonary resistance (c.g.s. units)	368	320	−13.0	18.22	0.05
Left ventricular work (Kg.-M./min.)	5.1	5.6	+9.8	0.529	0.3
Right ventricular work (Kg.-M./min.)	0.7	0.9	+28.6	0.125	0.2
Coronary blood flow (ml./100 Gm./min.)	99	114	+15.2	11.38	0.3
Left ventricular O_2 usage (ml./100 Gm./min.)	*10.3*	*12.7*	*+23.3*	*1.225*	*0.1*
Coronary vascular resistance	1.28	1.00	−21.9	0.089	0.02
Index of efficiency (LVW ÷ LV O_2 usage)	0.50	0.44	−12.0	0.047	0.3

crease in mean arterial blood pressure accompanied by tachycardia.[7] On closure of the fistula, opposite effects on these parameters were observed. In both cases the magnitude of the changes depended on the size of the fistula. Furthermore, after an early considerable change, there was gradual readjustment, tending back toward the control state but again, depending on the size of the fistula, generally remaining at a plateau short of complete readjustment. Although an attempt was made to keep the fistulas in each group uniform in size, a considerable spectrum of response was obtained because of variation in the healing process, the size of the animals, etc. The trends were quite clear, however, as described below.

The results, as summarized in Tables I and II, show the changes which occurred when the fistula was open; the controls in each case are the results obtained in the same animal with the fistula closed. The mean systemic arterial blood pressure decreased, whereas pulmonary arterial and right atrial mean pressures were increased; the increase was greater in those animals with large fistulas. Determinations of metabolism revealed narrowing of the arteriovenous difference for oxygen and carbon dioxide, whereas consumption of oxygen and excretion of carbon dioxide did not increase significantly, and the respiratory quotient was unchanged. The coronary sinus oxygen content decreased slightly, and the arteriocoronary sinus oxygen difference increased; similarly, there was an increase in coronary sinus–arterial carbon-dioxide difference. No change occurred in either arterial or coronary sinus pH. Cardiac output checked closely and increased significantly as measured by each method in the dogs with small fistulas; hence, only values obtained by the Fick principle are presented. Total peripheral and total pulmonary resistances decreased, whereas left and right ventricular work increased. Coronary blood flow increased, as did cardiac oxygen consumption. On the other hand, coronary vascular resistance (mean systemic arterial pressure divided by flow per 100 Gm. per minute) decreased significantly, whereas the index of cardiac efficiency, which relates oxygen consumption to cardiac work, was slightly but not significantly reduced.

Correlations were calculated, including all of the data from both the large and

Table II. Hemodynamic effects of aortocaval fistula

Parameter	*Fistula closed*	*Fistula open*	*% Change*	*Standard error of the mean*	*p Value <*
Heart rate (beats/min.)	133	182	+36.8	8.212	0.001
Mean arterial blood pressure (mm. Hg)	102	62	−39.2	5.586	0.001
Mean pulmonary arterial blood pressure (mm. Hg)	11	19	+72.7	1.061	0.001
Mean right atrial blood pressure (mm. Hg)	1.5	2.4	+60.0	0.395	0.2
Oxygen consumption (c.c./min.)	115	127	+10.4	6.554	0.1
Body respiratory quotient	0.86	0.86	——	——	——
Mixed venous oxygen content (ml./100 ml. of blood)	13.1	17.4	+32.8	0.645	0.001
Arteriovenous oxygen difference (ml./100 ml. of blood)	5.4	2.1	−61.1	0.376	0.001
Coronary sinus oxygen content (ml./100 ml. of blood)	4.0	3.1	−22.5	0.455	0.1
Arterial coronary sinus O_2 difference (ml./100 ml. of blood)	14.4	16.3	+13.2	0.654	0.02
Cardiac respiratory quotient	0.78	0.85	+9.0	0.019	0.01
Arterial hematocrit (%)	47	48	+2.1	1.500	0.6
Cardiac output (L./min.)	2.2	6.0	+172.7	0.409	0.001
Total peripheral resistance (c.g.s. units)	3,947	834	−78.9	514.8	0.001
Total pulmonary resistance (c.g.s. units)	424	256	−39.6	49.05	0.02
Left ventricular work (Kg.-M./min.)	3.1	5.2	+67.7	0.588	0.01
Right ventricular work (Kg.-M./min.)	0.3	1.6	+433.3	0.182	0.001
Coronary blood flow (ml./100 Gm./min.)	74	140	+89.2	7.856	0.001
Left ventricular O_2 usage (ml./100 Gm./min.)	10.5	22.4	+113.3	1.314	0.001
Coronary vascular resistance	1.40	0.47	−66.4	0.079	0.001
Index of efficiency (LVW ÷ LV O_2 usage)	0.30	0.24	−20.0	0.030	0.1

small fistulas. These calculations indicated that myocardial oxygen consumption was significantly and directly related to cardiac output ($r = +0.82$, $p < 0.001$), cardiac rate ($r = +0.63$, $p < 0.01$), and left ventricular work ($r = +0.42$, $p < 0.01$), inversely related to mean systemic arterial blood pressure ($r = 0.48$ p, < 0.01), and not significantly related to mean arterial blood pressure times rate ($r = +0.23$, $p > 0.1$). Coronary blood flow was directly related to cardiac output ($r = +0.67$, $p < 0.001$) and the left ventricular work ($r = +0.44$, $p < 0.01$), but not to rate ($r = +0.28$, $p < 0.1$), and inversely related to mean systemic arterial blood pressure ($r = -0.32$, $p < 0.05$). Under these circumstances the product of rate and mean systemic arterial blood pressure was not related to coronary flow ($r = +0.07$, $p > 0.1$). Coronary and peripheral vascular resistances were significantly related ($r = +0.66$, $p < 0.001$).

Discussion

The basic circulatory hemodynamics of experimental[1-10] and clinically occurring[11,12] arteriovenous fistulas, with their variable increase in cardiac rate and output and decrease in systemic arterial pressure, have been well described, and are confirmed in the present study. Data on coronary blood flow and myocardial oxygen consumption, however, have apparently been obtained only in the open-chest dog and are scattered. Thus, coronary flow as measured by the collection of coronary sinus blood through a Morawitz-Zahn cannula[3] or as determined by a differential pressure flowmeter in the coronary artery[4] was found to be reduced when the fistula was open, whereas the rotameter, measuring outflow from the coronary sinus, indicated increased flow.[5] The reason for this discrepancy is not apparent. Additional information also seemed to be desirable because of the data which indicated that opening of a small arteriovenous fistula is associated with an adequate compensatory increase in cardiac output,[9,13] but that the opening of larger fistulas is associated with a general reduction in blood flow through regions of the body other than that containing the fistula,[9,13] such as the vena cava, the femoral vessels, and the jugular vein opposite the site of the

fistula,[10] as well as through the kidney.[14,15] From the amount of change in blood pressure, it seems possible that the arteriovenous fistulas were too small to be hemodynamically significant in the human subjects who were reported to show no change in renal blood flow with opening and closing of the fistula.[16] The present study also revealed that the changes were minor and the adjustments less dramatic when the arteriovenous fistula was small. The trends were similar with both the small and the larger fistulas, however, and there seems to be no reason to complicate discussion by the uncertainties of marginal changes.

It is of considerable interest that in the present study, even though the systemic arterial pressure and total peripheral resistance were markedly reduced, the coronary vessels were able to decrease their resistance sufficiently so that coronary blood flow tended to increase in those dogs with small fistulas, and to increase significantly in those with large fistulas. Similar effects were reported previously for the coronary circulation of the open-chest animal,[5] and a similar reduction in the vascular resistance in the lower extremities has been reported to occur when an arteriovenous fistula is opened.[10] The present results afford a striking example of the ability of the normal coronary vessels to adjust to lowered arterial perfusion pressure, and negate mean arterial blood pressure as an overpowering determinant of coronary blood flow in the intact animal. Furthermore, under the present circumstance there is no relation between the product of mean arterial blood pressure and rate and either left ventricular oxygen consumption or coronary blood flow, even though this ratio has been found to be very useful in the nonintact animal.[17] Unfortunately, left ventricular pressures were not measured in these experiments, so that the integrated time pressure curve of the ventricle could not be determined. Hence, it is not known whether this index correlates with cardiac oxygen consumption under these conditions, as it does in the nonintact animal.[18] It should be noted that the per cent increase in rate almost exactly equals the per cent decrease in mean arterial blood pressure in each series, whereas the oxygen consumption of the left ventricle increased by 23 and 113 per cent, respectively, on opening of the small and large fistulas. These figures would seem to indicate that it is unlikely that the "time tension index" correlates with myocardial oxygen consumption significantly better in this experiment than does the product of mean arterial blood pressure and rate.

Accompanying the increase in cardiac work, induced by opening the fistula, was a significant increase in cardiac oxygen consumption. Indeed, the correlation between these two parameters is very significant ($p < 0.01$). It is obvious, of course, that mathematical correlation does not necessarily indicate physiologic dependence between variables, and it should be emphasized that other factors known to be related directly to cardiac oxygen consumption, such as rate, stroke volume, and cardiac output, are changed in the same direction and were also significantly correlated. We accept such interrelationships as those usually seen in the intact animal and man.[19]

Whereas in the present study there was an insignificant decrease in cardiac efficiency, a previous report indicated that efficiency was increased. This may well be a result of the fact that in the preceding study the experimental open-chest animals had undergone very extensive surgical procedures, and that their control cardiac rates were excessively high, with no significant increase in rate when the fistula was open.[5] The absence of tachycardia on opening of an arteriovenous fistula is very unusual, and the adverse influence on cardiac efficiency of increased cardiac rate without increase in output is sufficiently clear[20] that the question of the effect of an arteriovenous fistula on the efficiency of the heart requires reconsideration in the light of the present data. Surely, there can be no question as to the adverse effect of ateriovenous fistulas on the efficiency of the circulatory system as a whole. It is also true that increased cardiac output is so commonly associated with increased cardiac rate that no a priori statements in regard to the relationship of cardiac efficiency and output are justified.

Conclusions

1. A series of 11 dogs with chronic, single femoral arteriovenous fistulas, and 9 dogs with acute aortocaval fistulas have been studied by determination of cardiac output and coronary blood flow with the fistula open and closed.

2. Opening of the arteriovenous fistula in these animals was accompanied by decreased systemic arterial blood pressure, increased heart rate, increased cardiac output, and decreased total peripheral and pulmonary vascular resistance.

3. Coronary blood flow and myocardial oxygen consumption increased, and coronary vascular resistance decreased significantly.

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A simple device for the timing of individual films during angiocardiography

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The value of *angiocardiography in the* evaluation of congenital and acquired cardiovascular diseases, particularly when the contrast material is selectively injected into a cardiac chamber, is well established. One problem occasionally encountered when multiple roentgenograms are utilized rather than cine techniques is the precise timing of each exposure in relation to the cardiac cycle. In order to make a permanent record of the timing of each x-ray exposure during angiocardiography, we initially used an electronic circuit employing a "sun-battery," as suggested to us by Dr. Harold T. Dodge.[1] We have found, however, that for multiple exposures made at very short intervals more accurate timing of each exposure could be obtained by employing a vacuum tube photocell electronic circuit. It is the purpose of this communication to describe the circuitry developed for this purpose and to illustrate its use during selective angiocardiography.

The circuitry of our x-ray-sensitive timing marker (Fig. 1) consists basically of an RCA 934 photocell and a 6J6-6CL6 *amplifier with a Potter-Brumfield SM5LS* plate-operated relay in the 6CL6 output. The 6CL6 is biased to cut off by the 1N1083 diode bias supply. The 10K potentiometer serves to establish the operating point and should be set at the point at which the 6CL6 plate current stops. This point may be taken as about 0.5 to 1.0 volt greater than the setting at which the relay drops out. This voltage is approximately −15 volts. The closure time of the SM5LS and the response of the amplifier and photocell produces a delay of approximately 5 milliseconds in the closure of the relay after the exposure. A delay of this magnitude should be acceptable for general use, but can be corrected for if extremely precise timing is necessary. The 934 photocell* is wrapped in a piece of zinc sulfide fluoroscopic screen, and the cell and screen are then wrapped with black plastic electrical tape, which serves as a shield for extraneous light as well as for holding the screen in place. The photocell, wrapped in fluoroscopic screening and plastic tape, is then placed inside the housing of the x-ray tube, between the x-ray tube and shutter, far

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*A cadmium sulfide photocell was tried but proved to be inadequate because of a slow response time.

Fig. 1. Diagram of x-ray-sensitive timing circuit.

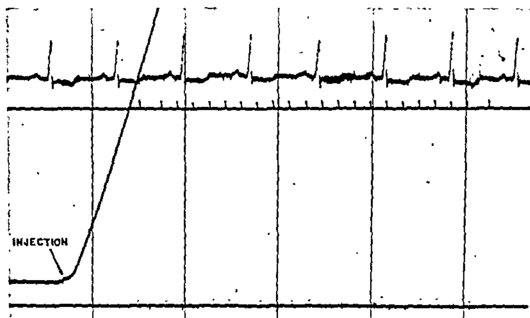


Fig. 2 Recordings made during injection of contrast material into the ascending aorta. *Upper tracing:* Electrocardiogram. *Middle tracing* Recordings of timing of individual angiocardiograms made at 6 per second. *Lower tracing.* Onset of motion of the plunger of the air-pressure injector of contrast material. Note the relatively long interval between the first and second exposures, a frequent finding with our Elema-Schonander apparatus. Paper speed is 50 mm. per second, and time lines are one per second.

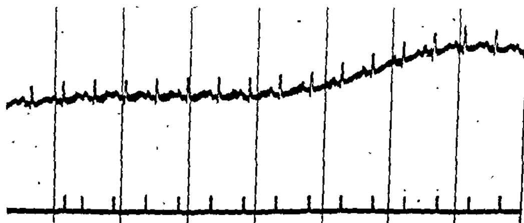


Fig. 3. Recordings made during injection of contrast material into the right ventricle *Upper tracing:* Electrocardiogram. *Lower tracing:* Timing of angiocardiograms at a rate of 2 per second. Note the absence of arrhythmia. In this instance the time between the first two exposures was considerably shorter than between subsequent exposures. Paper speed is 25 mm. per second, and time lines are one per second.

enough to one side so that it does not cast a shadow on the screen.

In use with an Electronics for Medicine DR8 recorder, the beams of a monitoring electrocardiograph channel and of the "marker" channel, which is connected by a two-lead phone jack to the leads indicated "EKG marker" and "ground" in Fig. 1, are positioned near each other in the center of the monitoring oscilloscope. Recording of the tracings at paper speed of 25 or 50 mm. per second is begun several seconds prior to the first exposure. Each x-ray exposure then produces, with a delay of only a few milliseconds, a small "blip" on the "marker" channel (Figs. 2-5). The timing of the exposure is then determined by comparison of the "marker" channel

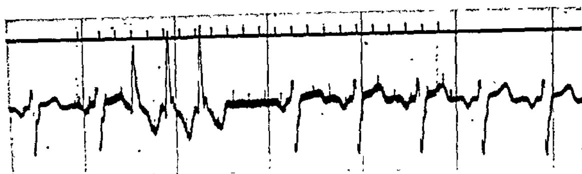


Fig. 4. Recordings made during injection of contrast material into the right ventricle. *Upper tracing:* Time markers which indicate the time of exposure of each film. *Lower tracing:* Electrocardiogram. Note the occurrence of three premature ventricular beats and the following long pause. In addition, there is an abnormally long interval between the first two exposures. Paper speed is 50 mm. per second, and time lines are one per second.

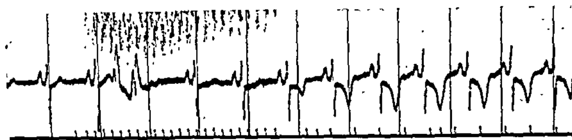


Fig 5 Tracings made during injection of contrast material into the right ventricle. *Upper tracing:* Electrocardiogram. *Lower tracing:* Timing "blips" which indicate exposures at a rate of 6 per second for 4 seconds, and then 2 per second for 6½ seconds. Note the two premature beats (beats number three and four) followed by a compensatory pause and the subsequent development of abnormal T waves in the electrocardiogram. In this instance there was a longer interval between the first two exposures when compared to the subsequent exposures, and during the later exposures at 2 per second there was considerable irregularity of exposures. Paper speed is 25 mm. per second, and time lines are one per second.

with the simultaneously recorded electrocardiogram. If desired, one may obtain even greater accuracy of timing in relation to cardiac events by comparing the timing of the electrocardiogram with the recordings of pressure in the cardiac chambers made just before or after the angiocardiogram. The electrocardiogram also serves to record any arrhythmias produced by the injection of contrast material.

If one desires to utilize a D.C. amplifier channel rather than a "marker" channel, a two-lead shielded cable may be run from the leads marked "100 mv. signal" and "ground" (Fig. 1) to the input of most D.C. amplifiers in use in catheterization laboratories.

Summary

An inexpensive and simple unit of electronic circuitry is described with which one may record precisely the timing of each film taken during angiocardiography, thereby improving the accuracy of interpreting each film in relation to the cardiac events.

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Effect of vanadium on serum cholesterol

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In vanadium workers over 40, Lewis[1] found that levels of serum cholesterol were significantly lower than in control subjects. Evidence of inhibition of cholesterol synthesis by vanadium compounds has been found in animals[2,3] and in healthy young men with a normal level of serum cholesterol.[4] Subsequent investigation suggested that vanadium was effective in lowering the level of cholesterol in patients with ischemic heart disease,[5] and it was decided to investigate this possibility further.

Material and methods

Twelve patients were treated with diammonium vanado-tartrate* for 6 months. The clinical data about the patients are summarized in Table 1. All patients were on a diet restricted in fat, and all but 2 (Cases 2 and 5) had established ischemic heart disease and were on long-term anticoagulant therapy. Nine patients had persistent hypercholesterolemia (serum cholesterol above 340 mg. per 100 ml.); in 7 of these the condition was familial, and 6 had xanthomatosis tendinosum.

Samples of blood for the estimation of serum cholesterol[7] and paper electrophoresis[8] were taken on three occasions before vanadium was started, monthly during the period of administration, and for 2 months after the drug was stopped. Samples were taken 1 to 2 hours after a fat-free meal. In 9 patients a qualitative test for vanadium in the urine was performed.[9] Before and during administration of the drug the blood urea and hemoglobin were estimated, and the urine was tested for albumin.

Diammonium vanado-tartrate was given in doses of 25 mg. three times daily during the first 2 weeks; the daily dose was raised to 125 mg. during the following fortnight and was maintained for a further 5 months in 10 patients. In 2 patients the drug was stopped during the fifth month because of toxic gastrointestinal effects.

Results

Statistical analysis of the results showed that there was no significant effect on serum cholesterol during administration of vanadium (Table I). There were no changes in the lipoprotein pattern, blood urea, or hemoglobin, and no patient developed albuminuria.

Five patients had persistent upper abdominal pain, anorexia, nausea, and loss of weight. Symptoms improved in 3 when the dose was reduced, and in the other 2 (Cases 4 and 8) the drug was stopped after 4 months. Green tongue[10] appeared in 5 men, and one other developed pharyngitis with marginal ulceration of the tongue.

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*Although they considered it unlikely that vanadium would be of value in lowering the level of cholesterol,[6] the Pharmaceutical Division of I.C.I., Ltd., agreed to make a suitable preparation.

Table I. Clinical and biochemical findings

Case	Age and sex	Condition present	Serum cholesterol before therapy (mg./100 ml.)	Serum cholesterol after therapy (mg./100 ml.)				
				1 mo.	3 mo.	4 mo.	5 mo.	6 mo.
1.	40, M	Ischemic heart disease. Angina: xanthomatosis tendinosum	458 425 495	484	463	—	433	495
2.	37, M	Xanthomatosis tendinosum	285 285 319	294	335	321	282	342
3.	64, F	Ischemic heart disease. Angina: xanthomatosis tendinosum	— 647 655	667	600	619	583	619
4.	59, M	Ischemic heart disease. Myocardial infarction. Angina: xanthomatosis tendinosum	408 406 473	420	392	—	395	381
5.	23, M	Familial hypercholesterolemia	386 347 410	333	309	365	425	357
6.	63, F	Ischemic heart disease. Angina. xanthomatosis tendinosum	414 420 399	427	438	441	—	443
7.	36, M	Ischemic heart disease. Angina: xanthomatosis tendinosum	— 487 504	557	—	495	504	504
8.	58, M	Ischemic heart disease. Angina: xanthomatosis tendinosum	457 451 450	386	367	409	401	423
9.	55, M	Ischemic heart disease. Myocardial infarction. Angina	— 388 363	382	390	371	—	381
10.	39, M	Ischemic heart disease. Angina	310 227 229	246	271	252	—	304
11.	56, M	Ischemic heart disease Angina	309 303 300	247	—	319	320	325
12.	61, F	Ischemic heart disease. Angina: hypertension	263 242 333	295	343	309	—	314

The negative results of this study are disappointing in view of the experience of other workers.[4,5] Curran[4] found a significant lowering of cholesterol only 6 weeks after vanadium was taken, but even in 3 of our patients who showed a slight reduction after 6 months (Cases 3, 4, and 8) no such trend was found early.

Vanadium was found in the urine of the 9 patients tested, which shows that the compound had been absorbed. However, no quantitative measurements were made, and it is possible that too little was absorbed to have a cholesterol-lowering effect.

Nine patients had hypercholesterolemia, and 6 of these had xanthomatosis tendinosum. It is possible that this type of patient has large stores of cholesterol which must be removed before reduction in serum cholesterol occurs. This might account for the fact that the results were different from those in Curran's normal people. There was no change in the size or shape of the xanthomata, which suggests that there was no mobilization of cholesterol from these sites.

The compound used in this study was the same as that described by Curran and his co-workers as diammonium oxy-tartrato vanadate.[4] Dimond[5] considered that vanadium should carry a valency of 5 to be effective, and that he had found the trivalent compound to be ineffective. Here, the tetravalent compound was used, as was the original vanadyl sulfate used by Curran on his liver slices.[2] Green[6] considered it unlikely that, once the compound was absorbed, it would matter whether it was tetravalent or pentavalent, and that it was possible that Dimond's trivalent compound was inadequately absorbed.

The clinical state of the patients remained unaltered except for one (Case 4) who developed cardiac infarction during the fourth month of observation.

Summary

Twelve patients were treated with oral vanadium for 6 months. Nine patients had hypercholesterolemia, and 7 of these had ischemic heart disease. Three patients had ischemic heart disease and normal serum cholesterol. No change in serum cho-

lesterol or lipoprotein patterns was found. The clinical course of the patients remained as would be expected for the natural history of the disease, and there was no alteration in the xanthomata. Toxic side effects occurred in 6 patients. In this limited study, therefore, we have found no evidence that diammonium vanadotartrate lowers serum cholesterol.

We thank Dr Paul Wood and Dr Lawson McDonald for their assistance in this study, Dr. K. G. Green and Dr. J. Thorp for their helpful cooperation, Imperial Chemical Industries, Limited, for kindly supplying the vanadium, and Dr. J. O. Irwin, Statistical Research Unit of the London School of Hygiene and Tropical Medicine, for statistical analysis of the readings of serum cholesterol.

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Experimental and laboratory reports

Arterial pressure and volume contour relations in man during aging

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In a preceding communication in this JOURNAL[1] we described differences in contour of pressure and volume pulses of the brachial artery in young subjects at rest. Pressure pulses were recorded by the use of classic techniques, whereas the volume pulses were recorded by a modification of segmental electrical impedance plethysmography; changes in impedance were recorded between the intra-arterial tip of an insulated Cournand needle and a single or multiple periarterial electrode. In these young persons the over-all area of the volume pulses exceeded the comparable area of equal-in-amplitude pressure pulses.

Very similar pressure-volume relations have also been described recently by Peterson and associates[2] in experiments on several arteries of anesthetized dogs, by the use of a more direct method for recording arterial diameter. Such data indicate the fundamental similarity of the physical properties of arterial segments in the two species; the type of strain response (change in size) of the arterial wall to the applied stress (intra-arterial pressure) obtained in both types of experiments indicates the presence of viscous elements, or of energy uptake by the wall during each cycle.

It has been considered necessary to extend these observations to older persons in order to detect changes of the viscoelastic properties of the wall which occur with advancing age. Therefore, in the present study, we investigated a group of older male subjects and compared them with a group of younger men; volume pulses were recorded by a further modification of the impedance technique employed in the previous study, which permitted a considerably better base-line stability and intraindividual pulse consistency.

The recorded pressure and volume pulses were compared simultaneously in a scalar and in a vectorial way. The scalar difference of the two pulses was continuously recorded through a subtracting amplifier; for the vectorial comparison, the two phenomena were connected with the Y and X plates of an independent cathode-ray tube, and the resultant Lissajous figure was photographed from the screen of the tube.

Subjects and methods

The experiments were performed on 16 young male "volunteer" students who were 16 to 28 years of age (mean of 22.8 years), and on 10 older men, some of whom were also "volunteers," and the rest of whom were inpatients who were being followed for various medical disorders. The ages of the latter subjects ranged from 50 to 75 years, with a mean of 62.9 years. All had normal sinus rhythm, and

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none was in heart failure at the time of the study. There was also no clinical evidence of arteriosclerotic disease in either brachial artery.

The subjects were studied in recumbency after a resting period of 30 to 60 minutes in a room in which the average temperature was 78 to 82 degrees Fahrenheit. The left arm was carefully positioned at the *cardiac zero* pressure level (10 cm. in front of the posterior chest wall) by the use of a soft arm support. The brachial artery at the elbow was punctured with a Cournand needle, which was connected with a 10-cm. long rigid polyethylene catheter (Clay-Adams PE-280) to either a Statham P23AA gauge (8 subjects) or a P23D gauge (16 subjects).

The natural frequency response of the system—needle-catheter-gauge—filled with fluid was 50 and 70 cycles per second, respectively, with the two gauges. Meticulous care was taken to eliminate all air bubbles from the system. Calibration with sinusoid pulses indicated that the response of the two systems was flat to well over 20 per cent of their respective natural frequencies. The pressure signals were observed and photographed on an Electronics for Medicine Research Recorder; the paper speed was 85 mm per second throughout.

Changes in impedance of the arterial segment were measured by using a "two-electrode" system (the same electrodes served as energizing and as recording elements) and a transistorized impedance plethysmograph* which operated on a carrier frequency of 30 kilocycles per second. The current from the oscillator was fed into a Wheatstone bridge, one leg of which included the impedance between the "two" arterial electrodes. The tip of the insulated Cournand needle was used as one electrode; the other "electrode" consisted of three interconnected hypodermic needles, insulated except for their tips, inserted around the artery as close as possible to the tip of the Cournand needle; they were carefully immobilized by tape after insertion. Changes of arterial capacity with each cycle resulted in changes in interelectrode impedance which unbalanced the Wheatstone bridge; these were rectified, filtered, and amplified through an ECG channel of the recorder. These changes were shown to reflect changes in arterial volume similar to those recorded by plethysmographic techniques.[3] The time-constant of the impedance amplifier *plus* connected ECG channel of the recorder was 1.5 seconds. The amplifier of the recorder channel had a frequency response flat from 0.1 to 100 cycles per second, and a cutoff rate of 6 decibels per octave at each end. The impedance pulses were calibrated by adding into the circuit a pure resistance of 0.3 ohms. This resistance was also used to determine the time-constant of the unit and connected amplifiers; in all records, an increased conductance (decreased resistivity) was indicated by an upward deflection.

Delay of the entire pressure pickup system with respect to the impedance system was checked in order to rule out instrumentally induced phase-angle differences between the two systems, which may account for loop figures on the cathode-ray screen (see below). This was 3.6 msec. as observed from transient oscillations with the needle, catheter, and electrodes connected to a saline-filled rubber tube. The fastest upstroke duration observed (either pressure or impedance) was 60 msec.; thus, maximal instrumental distortion could account for a phase shift of the rapidly ascending limb of the loop (see below) of less than one eighteenth of the upstroke.

Pressure-volume relations were continuously observed by connecting the output of the pressure amplifier to the Y axis, and the output of the impedance amplifier to the X axis of a cathode-ray oscilloscope. Thus, each cycle was recorded as a Lissajous loop, in conformity with similar findings in previous reports.[4] Selected typical loops were then photographed from the face of the tube. This method permitted the comparison of the pulse contours even when the amplitudes of the two pulses were not entirely equal; in fact, a mere increase or decrease in the size of the volume pulse, for example, would shift the loop down or up, respectively, without altering the relative position of its components.

Continuous recording of pressure-volume

*Parks Electronics, Aloha, Oregon

relations was also achieved by using an instantaneously subtracting amplifier and connecting the pressure pulse to its positive side, and the impedance pulse to its negative side. With the height of the impedance pulse adjusted to equal exactly that of the pressure pulse, the recorded difference between the two curves represented the relative difference in areas between the two contours. In each experiment, several pressure-impedance pulse doublets were recorded simultaneously, both as vector loops and as scalar phenomena, and are illustrated side by side. Determination of the exact area of corresponding pressure and impedance pulses was done by planimetry. The mean levels of pressure and volume were also obtained by this method. An average of 5 pulse doublets was studied in this way from each person.

Results

A. Differences in pressure pulses of young and old men. A definite increase in systolic pressure was observed in the older subjects (Table I). This was not associated

Table I. Means, standard deviations, and significance of differences (t-test, p-level) of brachial arterial pressure pulses in the two groups studied

Group	*Age (yr)*	*Pulse rate (per sec.)*	*Systolic pressure*	*Diastolic pressure*	*Mean level of pressure**	*Upstroke time*
Young (N:16)						
Mean	22.8	1.28	130.7	67.3	35.0	0.091
S.D.†	3.0	0.21	14.4	10.8	6.2	0.020
Old (N:10)						
Mean	62.9	1.12	167.2	71.9	38.6	0.136
S.D.	9.0	0.10	14.0	10.8	2.5	0.024
Significance of differences of means						
t		1.96	4.86	1.20	1.50	5.14
p		0.066	<0.001	0.20	0.15	<0.001

*Mean level of pressure (determined by planimetry) as a percentage of the pulse pressure (systolic minus diastolic pressure difference).
†S.D.: Standard deviation.

Table II. Means, standard deviations, and significance of differences of brachial arterial volume pulses in the two groups studied

Group	*Age (yr)*	*Pulse rate (per sec)*	*Upstroke time*	*Mean level of volume**	*Volume:pressure area*†
Young (N:16)					
Mean	22.8	1.28	0.109	44.3	120.0
S.D.‡	3.0	0.21	0.036	5.2	10.7
Old (N:10)					
Mean	62.9	1.12	0.103	34.3	91.4
S.D.	9.0	0.10	0.021	7.2	12.1
Significance of differences of means					
t		1.96	0.48	4.15	5.48
p		0.066	0.6	<0.001	<0.001

*Mean level of volume (determined by planimetry) as per cent of the maximal amplitude of the volume pulse.
†Ratio of areas of volume pulse in per cent of corresponding pressure pulses of equal amplitude.
‡S.D.: Standard deviation.

with a rise in diastolic pressure. The heart rate was slower in this same group, but the difference (0.16 of a pulse per second less in the older age group) does not reach the level of significance. A significant increase in the mean upstroke time from 0.090 second at the age of 23 to 0.136 second at the age of 63 is related to a slower rise in systolic pressure and a rounded and longer lasting systolic peak with age. These data are comparable to similar findings in the recent literature,[5] with the exception of the lack of a significant rise in diastolic pressure with age in our limited group.

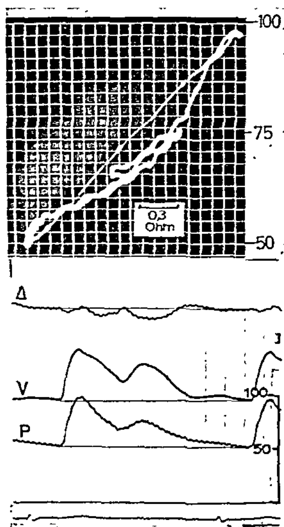


Fig. 1. In this and in Figs. 2, 3, and 4, the *upper* part represents the vectorial loop of the pulses pictured in the lower section. Changes in pressure are registered on the Y axis (calibration at the right), and changes in volume (impedance) on the X axis (calibration in 0.3 ohm). The cycle begins and ends at the lower left-hand corner, the upstroke is the thin line with time pips at 18-msec. intervals apart. The *lower* section, recorded simultaneously with the loop above it, contains the scalar pulses from the brachial artery of a 21-year-old man. *P* is the pressure pulse (Statham P23D gauge), and *V* is the impedance pulse, recorded as indicated in the section on methods. Calibration in millimeters of mercury and 0.3 ohm at the right. The upper line (Δ) is the instantaneous difference between the ordinates of the two pulses, *P* as positive, *V* as negative input.

The mean level of pressure, as indicated in Table I, is not statistically different in the two groups, although the respective levels for young and old are 35.0 and 38.6 per cent of the pulse pressure. This occurs despite a moderate decrease in the pulse rate in the aged, which would tend to reduce the mean level of the blood pressure. One should observe the small size of the standard deviation in the older age group; it indicates a uniformity of the pulse contours in this group which is lacking in the younger persons.

B. Volume pulses of young and old men. Table II presents data obtained from the arterial volume pulses in the two groups. It can be noted that the upstroke times do not differ between younger and older men, which finding is in contrast to the definite increase with age observed in the corresponding pressure pulses. Qualitative differences in pulse contour between the volume pulses of the two groups do exist, however, as indicated by the significant difference in the mean level of the volume pulses between young and old subjects. A decrease in the mean amplitude of the volume pulse occurs with age, from a level of 44.3 per cent of the height of the pulse at the age of 23 years to a level of 34.3 per cent at the age of 63 years. This indicates that volume pulses in the aged return faster to the base line from their maximal deflection.

As a result of this opposite trend in the mean levels of pressure and volume pulse areas, the ratio of areas of volume to pressure in pulses of equal amplitude decreased from a mean of 120.0 per cent (volume to pressure) to a mean of 91.4 per cent in the two age groups. This is highly significant (Table II) and cannot be attributed to the occurrence of higher systolic pressures in the older age group; in fact, within this group, the 4 persons with the highest systolic pressure (mean of 182 mm. Hg)

had also a significantly *higher* ratio of volume to pressure pulse (97.2 per cent) than did the 4 persons with the lowest systolic blood pressure (mean of 149 mm. Hg, ratio of volume to pressure significantly lower at 89.6 per cent).

C. Pressure-volume loops. In consequence of the above findings and of data reported by various authors[1,2,4,7] who used different methods for recording changes in arterial diameter, each cardiac cycle is represented as a clockwise-rotating loop in the young subjects; this occurs if the pressure is connected to the Y axis, and the volume to the X axis of the cathode-ray tube. Such a typical loop, with its component pulses, is presented in Fig. 1. The lower section represents the impedance (V) and pressure (P) pulses and their instantaneous difference (Δ). In the upper section the two pulses are combined as a loop; this is composed of a rapidly ascending straight section, from the lower left corner to the upper right, which corresponds to the simultaneous arterial distention and increase in pressure; a second, slower curvilinear part, which gradually returns to the origin, represents the remaining 95 per cent of the cycle, i.e., plateau, dicrotic notch, and diastole. It is evident that for any given level of pressure the volume (impedance pulse) is larger during the descent than it was during the ascent of pressure; this indicates that the artery displays viscosity during diastole, i.e., energy is absorbed by the wall. The additional looping segment within the downstroke is due to phase differences in the dicrotic notch between impedance and pressure pulses (pressure systole ends earlier than volume systole). These and other minor differences in contour between the two pulses can be clearly noted in the two pulses in the lower half of the figure. The subtraction curve between pressure and volume pulses (Δ) remains, in general, below the zero line; this is a quantitative expression of the preponderance of the area of volume over that of pressure, although maximal amplitudes of the two pulses are equal.

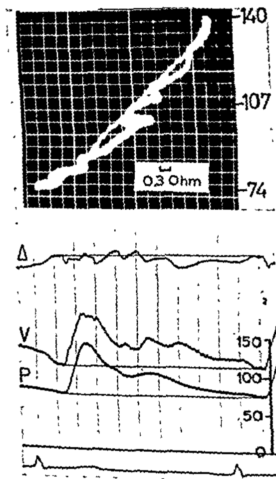


Fig. 2. As in Fig. 1, from a 22-year-old student. The ascending and descending segments of the loop follow each other closely, but both are transposed to the right of a straight line connecting the minimum and maximum of deflection. No time pips.

In Fig. 2, the ascent and descent follow each other closely, but both are transposed on a curve, to the right of a 45-degree line, which they should follow if the system were behaving according to Hooke's law. The scalar difference (Δ) between pressure and volume contours is small, but constantly negative, as discussed in Fig. 1. It should be noted that the increase in volume precedes the increase in pressure[1,2]; this is evident both in the initial swing of the loop to the right before its main upstroke and in the small negative swing of the curve of difference (Δ) of the pulse contours below.

Both Figs. 3 and 4 were obtained from the brachial arteries of elderly men—aged 75 years (Fig. 3) and 56 years (Fig. 4). There is a capital difference in both the loops and the scalar differences compared to the ones from the younger men, due to

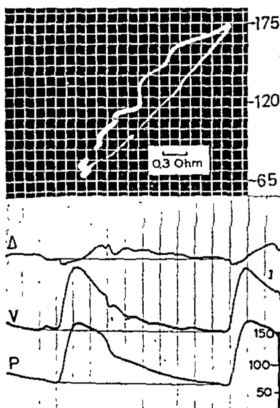


Fig. 3 As in Figs. 1 and 2, from a healthy 75-year-old man. The upstroke is linear, but the loop is rotated counterclockwise

the quantitative changes in the pressure and volume pulse contours with aging, as described above.

The loop of Fig. 3 is the opposite of that of Fig. 1. The upstroke of pressure is not prolonged in this case, so that the ascending limb of the loop is a linear function of pressure and volume. In contrast, the plateau, dicrotic notch, and diastolic phase are relatively larger in the pressure pulse than in the volume (impedance) pulse, so that the loop rotates in a counterclockwise fashion. Thus, for any given level of pressure the volume is smaller during the descent than it was during the ascent of pressure; stated otherwise, the arterial wall seems to contract during diastole, i.e., it appears to be stiffer and behaves as though it were forcing the blood. The lower half of Fig. 3 indicates these relations clearly and, moreover, shows that the subtraction curve (pressure minus volume) remains above the zero line during the major part of the cycle; this is the quantitative expression of the relative excess of the area of the pressure pulse throughout the cycle.

The loop of Fig. 4 is a typical example of prolonged upstroke of pressure with a short upstroke of volume; in consequence, the ascending limb of the loop is transposed to the left. Furthermore, the increase in volume occurs stepwise and trails the increase in pressure, so that periods of rise in *pure* pressure alternate with periods of rise in *combined* pressure and volume. Such would occur if frictional elements existed within the wall at one or more levels of distention, yielding only after variable absorption of energy from the blood during the rise in pressure; this energy is then released during diastole, when the size of the arterial segment decreases in a stepwise fashion, proportionately faster than the pressure. The total duration of pressure systole here exceeds slightly that of volume systole (compare with Fig. 1).

Part of the frictional behavior of the arterial wall depends on the neurogenic tone, as is suggested by Fig. 5, which was obtained from a 57-year-old patient. It shows a series of pressure-volume loops obtained at 30-second intervals from each other. Immediately after the second frame (from the left), 300 mg. of tetraethylammonium chloride were given intravenously; the decrease in pressure is obvious, as is the radical change in the loops, which become oriented clockwise, indicating a net gain in energy in the last three loops; they also indicate loss of *some* of the frictional steps which are present in the upstrokes of both control loops at the left.

Discussion

The designation of impedance tracings recorded herein as *arterial volume pulses* requires a short comment. The technique employed will measure changes in impedance in the entire interelectrode area, but, by keeping the interelectrode distance as small as possible, one can assume to record primarily cyclic changes in arterial capacity, if the thickness of the arterial wall remains constant; there is evidence that this is so.[7] A previous study[8] has indicated that differences between impedance pulses and conventional plethysmographic trac-

ings from the same superficial artery are only minor. It is obvious, of course, that these data cannot be directly translated into absolute units of diameter.

Further evidence that the present method does represent primarily arterial volumetric changes comes from comparison of the data obtained with two modifications of the impedance technique. We previously used[1] a skin electrode versus an intra-arterial electrode, or a single subcutaneous electrode versus the same intra-arterial electrode; by this method the mean ratio of volume to pressure areas was 127.3 per cent in a group of young persons which overlaps to a great extent the group employed in the present study. With the present method, which used three subcutaneous periarterial electrodes, the ratio was 120.0 per cent. Thus, whenever a skin electrode is employed, the volume pulse contour area is larger, probably from codetermination of changes in cutaneous vascular impedance. The present technique gives, in addition, significantly better base-line stability and day-to-day consistency of pulses, as indicated by a small number of cases in which repeated tests were made.

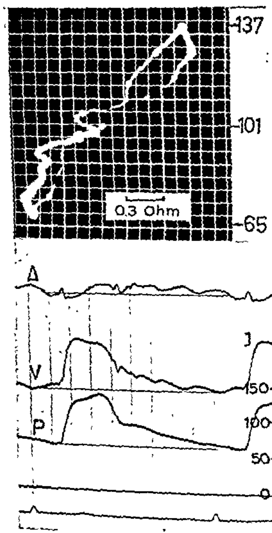


Fig. 4. Tracings from a 56-year-old man, indicating uneven distention and retraction which lead to a figure-of-eight-shaped loop, rotated counterclockwise. Both loop segments are transposed to the left of a straight line connecting minimum and maximum of distention.

One should further point out that the changes in volume pulse in the aged persons are not related to the existing higher systolic pressures or to the slower heart rates. It has been indicated above that the hypertensive subjects within the older age group had higher (more normal) volume to pressure ratios than did the normotensive subjects of the same group; however, a transient hypertension has been shown to reduce this ratio.[1] Thus, aging rather than hypertension was the factor responsible for the lower mean ratios in the elder men. Finally, the minor decrease in the mean heart rate in the elder group could account for a faster return of the volume pulse to the base line since its amplifier is AC-coupled. However, the relative excess of pressure over volume occurs throughout most of the cycle and not just during the end-diastolic phase (Figs. 3 and 4). The mean duration of diastole in this group of persons was 0.5 to 0.7 second; at these time intervals the distortion amounts to 6 and 17 per cent (at most) of the height of the steady-state diastolic level.

Our findings indicate a differential effect of aging upon the pressure (stress) and volume (strain) curves of the brachial artery. The effect on the pressure is that of a prolongation of upstroke and delayed return of diastolic level to the base line, i.e., a damping of the pressure wave; the effect on the volume (impedance) pulse is that of an acceleration of return to diastolic end-volume. Thus, the cyclic stress-strain relation of the brachial artery is altered from an energy-absorbing type to an

exception of the lack of some of the higher frequency oscillations observed by Peterson.

Finally, Wehn,[9] using a photocell, recorded changes in diameter of exposed, partly suspended femoral arteries in the rabbit. His data vary somewhat, depending upon the degree of elevation, but, in general, the diameter is shown to decrease twice within each cycle.

There are several instrumental differences between those studies[2,4,9] and the present one. The arterial sites examined are different, and in Rushmer's and Wehn's cases the longitudinal as well as the radial stress on the vessel must be sizable. Furthermore, the frequency response of the mercury-in-rubber gauge is low (flat to 3 per second[10]), so that during periods of rapid change of radius the volume-sensing system will tend to lag with respect to the pressure-sensing system; this will certainly distort the faster portions of the recorded loops.

The method employed herein to record changes in volume in the human being is admittedly, and by necessity, an indirect one. However, under identical local conditions, there is a significant difference in the orientation in space between the pressure-volume loops of the young men and those of the older men. This suggests either an action of the arteries "supportive" of the heart in the aged (analogous to the observations of Wehn[9]), or the occurrence of physical changes in the periarterial medium of the older persons, so that their impedance pulses possess a faster time of return to the base line. It is unfortunate that no additional comparative data on the ages of the dogs are given by Peterson and associates, other than in 2 of the 10. Additional data on older animals may have indicated whether the arteries of older dogs display the same qualitative differences, as suggested above for the arteries of older men.

Summary

In 16 healthy young men and 10 elderly men, pressure pulses from the left brachial artery were recorded through a Cournand needle, short stiff catheter, and a Statham P23AA or P23D gauge. Volume pulses from the same segment of the artery were recorded by amplifying the changes in impedance between the tip of the insulated arterial needle and three interconnected short needles, insulated to their tips, inserted around the artery at the level of the tip of the Cournand needle.

Recorded pressure and volume pulses were compared by automatic subtraction, and also by connecting them to the Y and X axes, respectively, of an additional cathode-ray tube; by this last method, each pulse described a loop figure on the screen.

In the group of young men the volume pulses exceeded in relative size the pressure pulses of equal amplitude (mean ratio of areas 120:100). Thus, a typical pressure-volume loop was a dextrorotated figure; the volume ordinates were proportionately larger than the pressure ordinates, especially during diastole. This was interpreted as indicating a viscous response (or storage of energy) of the arterial wall during late systole and diastole.

In the group of older men the pressure pulses had a longer upstroke time, higher systolic peak, and higher mean level of pressure (in per cent of the pulse pressure) than did the pressure pulses from the younger men. Volume pulses from the older men had identical upstroke times but a more rapid return to the diastolic end-volume than did similar pulses from young men. Thus, the mean level of the volume pulse was significantly lower in the aged, and the mean ratio of areas of volume pulses to pressure pulses of equal amplitude was 91:100.

Therefore, pressure-volume loops from elderly men were levorotated figures; the volume ordinates were proportionately smaller than the pressure ordinates, especially during diastole. This was interpreted as a release of energy from the wall during diastole.

The ascending limb of the loop in older men was frequently composed of periods of increase in pure pressure alternating with periods of increase in pressure *and* volume, i.e., showed evidence of friction; administration of a ganglionic blocking agent may convert such loops to grossly normal figures. This and other evidences suggest that there is increased parietal tension in the older men, or elevated periarterial tissue pressure, and that

parent stiffening of the wall may be altered by blocking neurogenic mechanisms.

Additional comparative studies on animals of different ages with direct methods of measuring arterial diameter are needed in order to extend the present observations in man.

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A method of isolated, gradual occlusion of a main branch of a coronary artery in closed-chest dogs

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The method used most frequently to occlude part of the coronary circulation in closed-chest dogs has involved the use of small plastic spheres, which were inserted by the Agress technique.[1] Mercury has also been used; it is injected either at the origins of the coronary arteries[2] or directly into them.[3] These techniques are adequate for acute experiments whereby a number of vessels of smaller caliber are blocked. Clinical infarction, however, usually follows the blockage of one of the larger vessels. As far as is known, gradual occlusion of a larger coronary vessel has not been accomplished without the aid of an open chest and direct approach to the heart. The present paper is a preliminary report of a new method of isolated, gradual occlusion of a main branch of a coronary artery in closed-chest dogs.

Methods

The experiments were carried out on dogs which had a body weight of 12 to 27 kilograms, and which were anesthetized with Pentothal sodium.

A special catheter with a detachable tip is introduced under fluoroscopic control into the left coronary artery from the carotid artery. The tip of the catheter, with a patent lumen, can then be separated off and left in the coronary artery. Ödman (Kifa) catheters are used, the tips of which are narrowed and divided 5 to 8 mm. from the end (Fig. 1). This separate tip is then affixed to a thinner catheter which is threaded through the outer one. By sliding the inner catheter back slightly, once the combined catheter is in place, the tip can be freed (Figs. 2 and 3).

In the first experiments, efforts were concentrated upon closure of the left coronary artery. Catheterization was carried out with the dog lying on the left side.

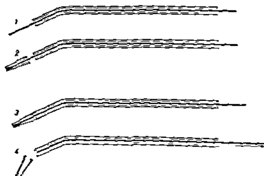


Fig. *1.* Catheter arrangement with free tip: *1* and *2* show the preparation of the catheter; *3* shows the final catheter arrangement before insertion, and *4* shows the separation of the tip after it is placed in the coronary artery.

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Fig. 2. Chest film showing the tip of the catheter in the circumflex branch of the left coronary artery



Fig. 3. Postmortem heart specimen of a dog sacrificed shortly after the tip of the catheter was inserted into the descending branch of the left coronary artery.



Fig. 4. Anterior wall of the heart of a dog sacrificed 28 days after gradual closure of the ramus descendens. The arrow shows the locus of the catheter tip, the vessel having been freed at this site. In the region of the left ventricle, near the apex, a locus of adherent pericardium was present, covering the site of infarction. The photograph shows the adherent segments of pericardium above this area.

When the catheter was introduced into the descending artery, the tip was oriented toward the sternum, whereas when the cathether was inserted into the circumflex artery, the tip had to be oriented posteriorly. Patency of the tip was verified by angiography. This was carried out before catheterization, and 30 minutes and 1, 2, etc., weeks after catheterization, either with acetylcholine-induced cardiac standstill[4] or by x-ray kinematography. The electrocardiogram was recorded at the same time intervals (standard and three unipolar chest leads at the level of the apex).

Results

The experiments were carried out in 35 dogs. The tip of the catheter was successfully placed in 31 of these. In 4 animals the catheter could not be introduced, in 2 of which the postmortem examination revealed an anomalous origin of the left coronary artery. The circumflex artery was blocked in 21 animals, and the descending artery in 9 animals; in 1 animal two tips were introduced, one into the circumflex artery and one into the descending artery. The first 2 animals were sacrificed 1 hour after the tip of the catheter had been inserted. Five dogs died from 6 to 35 minutes after insertion, and 2 dogs died 3 hours later. The cause of death was ventricular fibrillation, in one case during coronary angiography while the heart was in acetylcholine standstill, carried out exceptionally 6 minutes after insertion. In all the dogs which died shortly after the experiment the electrocardiogram showed signs of an acute infarction shortly after the tip of the catheter had been inserted. Twelve dogs survived the acute stage and died from 12 to 52 hours later. None of these showed electrocardiographic signs of infarction 30 minutes after insertion of the tip. However, these animals all showed, on postmortem examination, thrombotic closure of the coronary vessels which contained the tip, and there were histologic signs of the initial stages of infarction in the region of myocardium supplied by the embolized vessel. Ten dogs

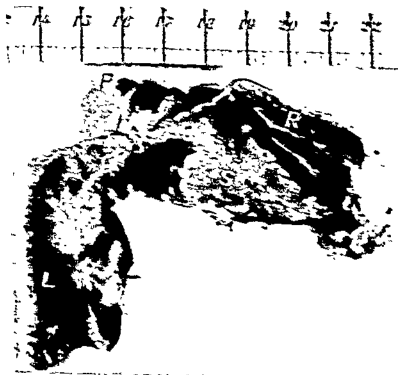


Fig. 5. Cross-section of the ventricular wall of the heart shown in Fig. 4, taken through the site of infarction. Thinning of the wall can be seen, along with a portion of the adherent pericardium (P). Note the difference in coloration of the muscle. L: Left ventricular wall. R: Right ventricular wall. S: Septum.

survived for more than 1 week. Two of the latter died after 8 days, and another 2 were sacrificed after 4 to 5 weeks. The above-mentioned 4 dogs showed microscopic and macroscopic signs of infarction; the latter are illustrated by Figs. 4 and 5. Observations were continued on 6 dogs which were still surviving several months later.

Discussion

The method described enables the main branches of the coronary arteries to be closed off less abruptly than by ligation, without opening the thorax for manipulation, and permits chronic investigation of the effects of myocardial infarction in the closed-chest dog. The coronary lumen is acutely narrowed internally to simulate an atherosclerotic plaque, and then is gradually closed off by thrombosis. This method makes it possible to produce a model of coronary occlusion and to study surgical and medical procedures intended to improve revascularization, without the complication of a previous thoracotomy. A combination of this method with the injection of small plastic spheres might serve to approximate existing conditions in man.

Summary

A method of gradual closure of the left coronary artery or its main branches in the closed-chest dog has been described. The method consists of using a concentric catheter arrangement, by which means a short catheter tip with a patent lumen can be inserted.

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Preventive effectiveness of MAO inhibitor and ineffectiveness of prothrombinopenic anticoagulant against increase in plasma thrombin activity by adrenaline, cholesterol, and traumatization

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The authors found that monoamine oxidase (MAO) inhibitors prevent powerfully the appearance of thrombosis induced experimentally by traumatization of the internal surface of blood vessels in rabbits without inhibiting extravascular clotting, and that they are much stronger than anticoagulants tested in such an experimental condition.[1,2] The authors[3] also found that MAO inhibitors prevent the acute vascular reaction which is specifically induced by adrenaline in a dose of physiologic significance, but not in a large dose, or by cholesterol. The reaction consists of an acute edematous abnormality of the blood vessel wall, involving fractionation of elastic fibers and adherence of platelets and leukocytes to the endothelial surface, accompanied by a decrease in Moolten and Vromen's adhesive platelet count as well as a shortening of the coagulation time of whole blood.

In this experiment on rabbits the shortening of the one-stage prothrombin time induced by adrenaline[5] or cholesterol[6] or traumatization of the internal surface of blood vessels was subjected to testing of the preventive effect of phenindione, an anticoagulant, and of nialamide, a MAO inhibitor. It was found that nialamide prevents the shortening and that phenindione does not prevent it.

Material and method

Two hundred and eighty male rabbits which weighed between 1.8 and 3.0 kilograms (2.3 ± 0.5 kilograms) were subjected to the experiment. The room temperature was 23 to 28 degrees centigrade. The one-stage prothrombin time of the blood was measured before and after the challenges by modified Quick's method, using thrombokinase with calcium,* because of the reproducibility and the clear-cut end point of the test in the case of rabbits. The specimens of blood were taken from the marginal vein of the ear of both sides, using siliconized syringes.

Modified Quick's method.

REAGENTS. Suspension of thrombokinase: One tablet was placed in a thick-walled test tube and carefully crushed to a fine

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*Produced by Geigy Company.

powder with a glass rod. Two drops of distilled water were added and stirred with the powder to form a smooth paste. To this were added 2.5 ml. of distilled water, and the contents of the tube were thoroughly mixed. The suspension was warmed to 37.0°C. for 15 minutes. The preparation was then ready for use. *Isotonic solution of sodium citrate:* Trisodium citrate dihydrate (sodium citrate B.P.: $C_6H_5O_7Na_3, 2H_2O$), 3.13 Gm., was dissolved in distilled water and made up to 100 ml.

TAKING THE SAMPLE OF BLOOD. Eight tenths of a milliliter of blood was taken by venepuncture and mixed in the syringe with 0.2 ml. of an isotonic solution of sodium citrate. The sample was then centrifuged at 1,700 r.p.m. for 7 minutes, and the plasma was separated from the deposit of red cells. According to Geigy's recommendation, the determination of prothrombin-time should be carried out within 2 hours after the sample is taken. We performed the determination 1 hour after each test specimen had been obtained. The specimens were kept in the refrigerator at a temperature of +4°C. until the test.

Determination of prothrombin-time. One tenth of a milliliter of plasma was placed in a test tube, 10 to 11 cm. in length and 9 to 11 mm. in diameter, which was then warmed for 2 minutes in a water bath at 37.0°C. The thrombokinase-suspension was also warmed to the same temperature. Before it was used, the suspension was thoroughly mixed by means of air bubbles blown in from the pipette. To the 0.1 ml. sample of plasma, 0.2 ml. of the warm thrombokinase-suspension was rapidly added (the pipette was blown out but was not allowed to touch the plasma); at the same moment a stopwatch was set in motion, and the time that elapsed before the plasma solidified was measured. In rabbits the visible endpoint with this test was clear cut, whereas in men this differs because of the prolonged prothrombin time. The determination was repeated until two measurements agreed to within 0.5 second; the mean of the two was taken as the prothrombin time. Usually, just the first and second measurements agreed to within at least 0.3 second.

Needless to say, the perfect blind technique is important in this kind of measurement; the one-stage prothrombin time was measured by a technician who had no information on the character of the specimens of blood taken.

Forty rabbits were subjected to the control experiments. An empty gelatin capsule was given to 10 of them, and an injection of 1 ml. of physiologic saline was made in another 10; then the one-stage prothrombin time of the blood was measured before and at 30 minutes, 1, 2, 3, and 12 hours after the administration of the gelatin capsule, and at 5 and 30 minutes and 1, 2, and 12 hours after the saline. The capsule was easily swallowed by the rabbits when it was gently inserted into their throat by a pincette. One-shot treatment of animals with several doses of noradrenaline and with a large dose, e.g., 100 μg per kilogram, of adrenaline, differing from a small dose of adrenaline, were found by the authors[3,4] not to induce the acute edematous vascular reaction and not to shorten the coagulation time of whole blood in rabbits. For such reasons, noradrenaline in a dose of 1 μg per kilogram was administered in 10 animals, and adrenaline in a dose of 100 μg per kilogram was also administered intravenously in the other 10 animals; then the one-stage prothrombin time of these 20 animals was measured before and at 5 and 30 minutes and 1, 2, and 12 hours after the administration of these substances also as a control experiment.

The challenge with adrenaline was performed in 15 control animals and in 15 animals pretreated with nialamide; the adrenaline was injected intravenously into the marginal vein of the ear which was utilized for taking the control specimen of blood but not for taking the specimen after the challenge. The dose was 1.0 μg per kilogram diluted with saline to become 2 μg per 1 ml. immediately before each experiment. The specimens of blood were taken before and at 5 and 30 minutes and 1, 2, and 12 hours after the injection of adrenaline for the measurement of the one-stage prothrombin time.

The challenge with cholesterol was performed in 15 control animals and in 15 animals pretreated with nialamide; 1 Gm. per kilogram of cholesterol which was

packed in a gelatin capsule was given orally. The specimens of blood were taken before and at 30 minutes, 1,2,3, and 12 hours after the administration of cholesterol for the measurement of the one-stage prothrombin time.

The challenge by traumatization of the internal surface of blood vessels was performed in 15 control animals and 15 animals pretreated with nialamide. Traumatization was accomplished with a No. 6 dental hand reamer which was inserted into the retroauricular artery 3 cm. in length; the artery was held between a type of paper holder with a weak spring and then the reamer was pulled out. The specimens of blood were taken before and at 5 and 30 minutes and 1,2, and 12 hours after the challenge for the measurement of the one-stage prothrombin time.

The same series of experiments were performed on the other 150 animals; 75 of these animals were pretreated with 400 mg. of phenindione at 48 hours, and an additional 200 mg. at 24 hours, before the challenge, and the other 75 animals were pretreated with the same dose of phenindione and, at the same time, with nialamide. Nialamide was administered in a dose of 5 mg. per kilogram by mouth 2 hours before each challenge. There were 25 animals in each series of this experiment with adrenaline, cholesterol, or traumatization.*

Results

In the control experiments, the one-stage prothrombin time measured after the administration of an empty gelatin capsule in 10 animals and of saline in 10 animals was found to exhibit no significant difference as compared with the value measured before the procedure in each animal.

Before the challenge with the empty gelatin capsule the mean value and the standard error for 10 animals was 10.0 ± 0.1 seconds; after the challenge the values were 10.0 ± 0.1, 9.9 ± 0.1, 10.0 ± 0.1, 10.0 ± 0.1, and 9.9 ± 0.1 seconds at 30 minutes, 1, 2, 3, and 12 hours, respectively (Fig. 1,*A*). Before the challenge with the saline the mean value for 10 animals was 10.1 ± 0.1 seconds; the values were 10.0 ± 0.1, 10.1 ± 0.1, 10.0 ± 0.1, 10.0 ± 0.1, and 10.1 ± 0.1 seconds at 5 minutes, 30 minutes, 1, 2, and 12 hours after the administration of saline, respectively (Fig. 1,*B*). As shown in Fig. 1,*C*, the one-stage prothrombin time was not significantly shortened by the injection of 1 μg per kilogram of noradrenaline; the mean value before noradrenaline was 10.2 ± 0.1 seconds, and after noradrenaline the values were 10.1 ± 0.1, 10.2 ± 0.1, 10.2 ± 0.1, 10.6 ± 0.2, and 10.2 ± 0.1 seconds at 5 minutes, 30 minutes, 1, 2, and 12 hours, respectively. As shown in Fig. 1,*D*, the one-stage prothrombin time was not significantly shortened by the injection of 100 μg per kilogram of adrenaline. The mean control value was 10.0 ± 0.2 seconds; the values were 9.9 ± 0.1, 10.3 ± 0.1, 10.1 ± 0.2, 10.1 ± 0.1, and 10.0 ± 0.1 seconds at 5 and 30 minutes and 1, 2, and 12 hours after adrenaline, respectively.

As shown in Fig. 2,*A*, the one-stage prothrombin time was shortened significantly by the administration of 1μg per kilogram of adrenaline. The mean control value for all 15 animals was 10.0 ± 0.1 seconds, and after the administration of adrenaline the mean values were 8.6 ± 0.3, 9.4 ± 0.3, 10.5 ± 0.2, 10.4 ± 0.2, and 10.1 ± 0.2 seconds at 5 and 30 minutes and 1, 2, and 12 hours, respectively. The shortening at 5 minutes after adrenaline is statistically significant ($p < 0.01$).

As shown in Fig. 2,*B*, the one-stage prothrombin time was not shortened by the administration of the same amount of adrenaline in all 15 animals pretreated with nialamide ($p < 0.01$). The mean control value for all 15 animals was 10.0 ± 0.1 seconds, and the values after the administration of adrenaline were, respectively, 10.0 ± 0.1, 10.0 ± 0.2, 10.0 ± 0.2, 10.0 ± 0.1, and 10.2 ± 0.2 seconds at 5 and 30 minutes and 1, 2, and 12 hours.

As shown in Fig. 2,*C*, the one-stage prothrombin time for all 25 animals pretreated with phenindione exhibited significantly a prolongation which amounted to 18.2 ± 1.3 seconds and ranged from 12.9 to 30.2 seconds, but after the administration of adrenaline it was shortened significantly.

*The adrenaline used was produced by Sankyo Company. The noradrenaline was Levophed from the Winthrop Company. The cholesterol used was produced by Taiyo Company. The MAO inhibitor was Niamid produced by Chas. Pfizer Company. The phenindione used was Indion produced by Daiichi Pharmaceutical Company

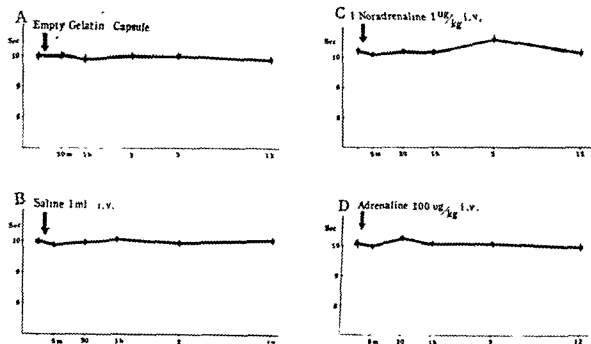


Fig. 1. Control experiments. The mean one-stage prothrombin time with the standard error for each of 10 animals treated by oral administration of empty gelatin capsule (*A*) and by intravenous injection of physiologic saline (*B*), 1 μg per kilogram of noradrenaline (*C*), and 100 μg per kilogram of adrenaline (*D*) is shown in the course of time before and after the treatment. No change is seen with these challenges.

The mean values for all 25 animals were 14.8 ± 0.9 ($p < 0.05$), 19.1 ± 1.3, 19.8 ± 1.2, and 20.8 ± 1.2 seconds at 5 and 30 minutes and 1 and 2 hours after adrenaline, respectively.

As shown in Fig. 2,*D*, the one-stage prothrombin time of all 25 animals pretreated with phenindione and nialamide exhibited no shortening ($p < 0.01$). The mean control value was 23.6 ± 1.8 seconds, ranging from 13.4 to 31.0 seconds; the values after adrenaline were 23.2 ± 1.8, 23.2 ± 1.9, 23.0 ± 1.9, and 24.0 ± 1.9 seconds, respectively, at 5 and 30 minutes and 1 and 2 hours.

As shown in Fig. 3,*A*, the one-stage prothrombin time was significantly shortened by the administration of 1 Gm. per kilogram of cholesterol. The mean control value for all 15 animals was 10.1 ± 0.2 seconds; after cholesterol the values were 9.5 ± 0.2, 8.8 ± 0.1, 10.2 ± 0.1, 10.3 ± 0.2, and 9.8 ± 0.2 seconds at 30 minutes, 1, 2, 3, and 12 hours, respectively. The shortening 1 hour after cholesterol is statistically significant ($p < 0.01$).

As shown in Fig. 3,*B*, the one-stage prothrombin time of all 15 animals pretreated with nialamide was not shortened by cholesterol. The mean control value for 15 animals was 9.8 ± 0.1 seconds; the values were 9.6 ± 0.3, 9.8 ± 0.2, 9.8 ± 0.2, 9.7 ± 0.2, and 9.6 ± 0.2 seconds at 30 minutes, 1, 2, 3, and 12 hours after cholesterol, respectively.

As shown in Fig. 3,*C*, the one-stage prothrombin time was powerfully prolonged in animals pretreated with phenindione, but the administration of cholesterol exhibited a significant shortening. The mean value for all 25 animals pretreated with phenindione was 21.6 ± 1.6 seconds, ranging from 13.5 to 30.0 seconds; after cholesterol the values were 17.8 ± 1.8, 15.7 ± 1.2, 16.6 ± 1.9, and 19.7 ± 1.9 seconds at 30 minutes and 1, 2, and 3 hours, respectively. The shortening 1 hour after cholesterol is statistically significant ($p < 0.05$).

As shown in Fig. 3, *D*, the one-stage prothrombin time of all 25 animals pretreated with phenindione and nialamide was not shortened by cholesterol ($p < 0.01$). The mean control value for all 25 animals was 18.4 ± 0.7 seconds, ranging from 14.0 to 30.0 seconds; after

cholesterol the values were 18.4 ± 0.6, 18.3 ± 0.7, 17.9 ± 0.7, and 18.0 ± 0.8 seconds at 30 minutes and 1, 2, and 3 hours, respectively.

As shown in Fig. 4,*A*, the one-stage prothrombin time of all 15 animals was significantly shortened by traumatization. The mean control value for all 15 animals was 9.9 ± 0.2 seconds; the values after traumatization were 8.0 ± 0.3, 7.0 ± 0.1, 9.3 ± 0.2, 9.7 ± 0.1, and 9.7 ± 0.1 seconds at 5 and 30 minutes and 1, 2, and 12 hours, respectively. The shortening at 5 and 30 minutes after traumatization is statistically significant ($p < 0.01$).

As shown in Fig. 4,*B*, the one-stage prothrombin time of all 15 animals pretreated with nialamide was not shortened by traumatization. The mean control value was 9.9 ± 0.1 seconds, and the values after traumatization were 9.8 ± 0.2, 10.2 ± 0.1, 10.2 ± 0.1, 10.1 ± 0.1, and 10.1 ± 0.1 seconds at 5 and 30 minutes and 1, 2, and 12 hours, respectively.

As shown in Fig. 4, *C*, the one-stage prothrombin time of all 25 animals pretreated with phenindione exhibited a marked prolongation, but it was significantly shortened by traumatization of the internal surface of blood vessels. The mean control value was 22.5 ± 1.9 seconds, ranging from 13.2 to 34.0 seconds; the values were, respectively, 17.2 ± 1.5, 18.8 ± 1.9, 20.4 ± 1.4, and 15.7 ± 0.2 seconds at 5 and 30 minutes and 1 and 2 hours after traumatization. The shortening at 5 minutes and 1 hour after traumatization is statistically significant ($p < 0.05$).

As shown in Fig. 4,*D*, the one-stage prothrombin time of all 25 animals pretreated with phenindione and nialamide was not significantly shortened by traumatization of the internal surface of blood vessels. The mean control value for all

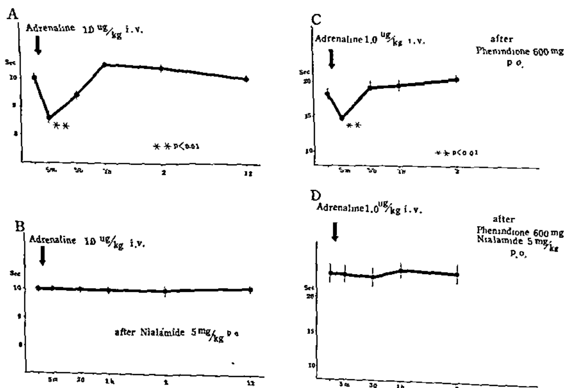


Fig. 2. The mean one-stage prothrombin time with the standard error for animals treated with intravenous injection of 1 µg per kilogram of adrenaline is shown in the course of time before and after the treatment. The first group of 15 animals received no pretreatment (*A*). The second group of 15 animals were pretreated with 5 mg. per kilogram of nialamide (*B*). The third group of 25 animals were pretreated with 600 mg. of phenindione (*C*). The fourth group of 25 animals were pretreated with 5 mg. per kilogram of nialamide and 600 mg. of phenindione (*D*). The preventive effectiveness of nialamide and the ineffectiveness of phenindione against the shortening of one-stage prothrombin time by 1 µg per kilogram of adrenaline are seen.

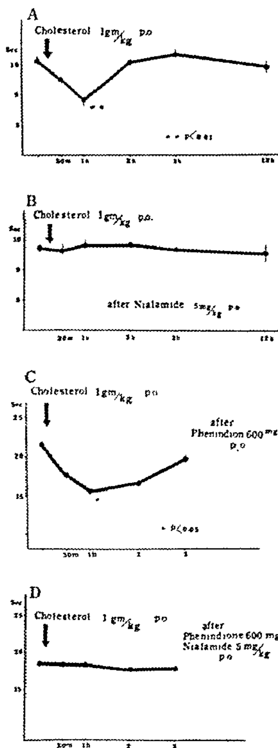


Fig. 3. The mean one-stage prothrombin time with the standard error for animals treated by oral administration of 1 Gm. per kilogram of cholesterol is shown in the course of time before and after the treatment. The first group of 15 animals received no pretreatment (*A*). The second group of 15 animals were pretreated with 5 mg. per kilogram of nialamide (*B*). The third group of 25 animals received pretreatment with 600 mg. of phenindione (*C*). The fourth group of 25 animals were pretreated with 5 mg. per kilogram of nialamide and 600 mg. of phenindione (*D*). The preventive effectiveness of nialamide and the ineffectiveness of phenindione against the shortening of the one-stage prothrombin time by 1 Gm. per kilogram of cholesterol are seen.

25 animals was 21.2 ± 1.5 seconds, ranging from 15.6 to 38.4 seconds; after traumatization the values were 20.7 ± 1.5, 20.5 ± 1.8, 21.6 ± 1.9, and 21.8 ± 1.6 seconds at 5 and 30 minutes and 1 and 2 hours, respectively.

Discussion

In the same kind of experiments, other MAO inhibitors, such as iproniazid, isocarboxazid, pheniprazine, and phenelzine, and another prothrombinopenic anticoagulant, warfarin, were also tried. The preliminary data indicate also the preventive effectiveness of these other MAO inhibitors and the ineffectiveness of warfarin.

Adrenaline, in a dose of physiologic significance, and cholesterol were found by the authors[3] to produce, in rabbits, an edematous vascular reaction which was accompanied by a fractionation of elastic fibers and adherence of platelets and leukocytes to the endothelial surface[3] (findings made by means of an electron microscopic technique). Also, the coagulation time of whole blood, measured by Fonio's method, and the adhesive platelet count, measured by Moolten and Vroman's method, were found to exhibit a concomitant reduction during the reaction.[3,4] MAO inhibitor was found[3,4] to inhibit significantly these reactions induced by adrenaline and cholesterol.

The results obtained in this experiment are entirely in accord with those findings. The most important finding in this experiment was the ineffectiveness of phenindione in preventing the shortening of prothrombin time induced by the challenges used.

The mechanism involved in the shortening of the coagulation time of whole blood as well as of the one-stage prothrombin time by adrenaline, cholesterol, or traumatization of the blood vessels is beyond the scope of this experiment. However, such challenges were found to induce

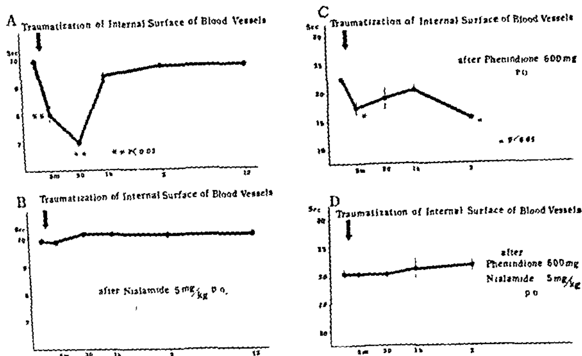


Fig. 4. The mean one-stage prothrombin time with the standard error for animals treated by traumatization of the internal surface of blood vessels is shown in the course of time before and after treatment. The first group of 15 animals received *no pretreatment* (*A*). The *second group* of 15 animals were pretreated with 5 mg. per kilogram of nialamide (*B*). The third group of 25 animals were pretreated with 600 mg. of phenindione (*C*). The fourth group of 25 animals were pretreated with 5 mg. per kilogram of nialamide and 600 mg. of phenindione (*D*). The preventive effectiveness of nialamide and the ineffectiveness of phenindione against the shortening of one-stage prothrombin time by traumatization of the internal surface of blood vessels are seen.

the adherence of platelets to the endothelial surface as well as the edematous reaction of the vessel walls, with a typical fractionation of elastic fibers along their collagen filaments, as described above.[3] Moreover, the authors have found that the intravenous injection of 1 μg per kilogram of noradrenaline, and also of 100 μg per kilogram of adrenaline, into rabbits does not induce the afore-mentioned reactions and, at the same time, does not shorten the one-stage prothrombin time. For such reasons, the shortening of one-stage prothrombin time by the challenges performed in this experiment may be attributable to the edematous vascular reactions to these challenges; under such conditions the platelet factor may be released from the aggregated platelets, or tissue thromboplastin may be released from the endothelial cells into the blood stream, and such factors may contribute to the shortening of the coagulation time of the blood.

Pretreatment of animals with MAO inhibitors has been found by the authors to prevent the adherence and aggregation of platelets and also, powerfully, the acute edematous vascular reaction by the above-mentioned challenges, and such effects of nialamide may account for its prevention of the shortening of the one-stage prothrombin time by the above-mentioned challenges.

On the other hand, prothrombinopenic anticoagulant, even in a large dose, was found not to prevent the shortening of the one-stage prothrombin time of the blood induced by the above-described challenges, and was also found not to prevent the acute edematous vascular reaction by these challenges in the other experiment.

Summary and conclusions

Adrenaline in an intravenous dose of 1.0 μg per kilogram was found to induce a significant shortening of the one-stage prothrombin time not only in 15 normal

rabbits ($p < 0.01$) but also in 25 rabbits pretreated with 600 mg. of phenindione with a marked prolongation of the prothrombin time ($p < 0.05$).

Cholesterol in an orally administered dose of 1 Gm. per kilogram was also found to shorten significantly the one-stage prothrombin time not only in 15 normal rabbits ($p < 0.01$) but also in 25 rabbits pretreated with 600 mg. of phenindione ($p < 0.05$).

Traumatization of the internal surface of the retroauricular artery was also found to shorten significantly the one-stage prothrombin time of all 15 normal rabbits ($p < 0.01$) as well as of 25 rabbits pretreated with 600 mg. of phenindione ($p < 0.05$).

The shortening of the one-stage prothrombin time by these three challenges was not found in animals pretreated with 5 mg. per kilogram of nialamide 2 hours beforehand, neither in 45 normal rabbits nor in 75 which were pretreated with 600 mg. of phenindione with a prolongation of the prothrombin time ($p < 0.01$).

The MAO inhibitor nialamide was found to exert a clear-cut preventive effect against the shortening of the one-stage prothrombin time induced by the administration of adrenaline or cholesterol or by traumatization of the internal surface of blood vessels of rabbits; on the other hand, the prothrombinopenic anticoagulant phenindione was found not to exert such a preventive effect.

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A comparison between ultralow-frequency ballistocardiograms and those secured by an improved high-frequency technique, with studies to explain remaining differences

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The advance in ballistocardiographic instrumentation which has been so rapid and so encouraging in recent years has been due primarily to the use of certain physical principles. On the assumption that well-known physical formulae could be properly applied to the vibration problems of the human body, a new viewpoint emerged. This included a well-based criticism of the high-frequency (HF) ballistocardiograph,[1,2] i.e., that the movement which took place between body and table was introducing an error, and that the vibration properties of this movement between body and table led to an undue magnification of certain components of the recorded forces, those delivered in resonance with the body's own vibration properties, and undue attenuation of others, those above the body's resonance frequency. It was proposed to avoid or minimize such errors by using another type of instrument, the ultralow-frequency (ULF) ballistocardiograph.[3-6]

The very considerable technical problems were overcome in a number of laboratories, and several types of excellent ultralow-frequency ballistocardiographs have been constructed; these differ only in technical details and give essentially similar records. With this experience before us the instrument used in this study was constructed by Mr. George Peirce.

The possession of such an instrument permitted us to compare force ballistocardiograms taken by the ultralow-frequency technique, when acceleration of the table is recorded, with force ballistocardiograms taken with the high-frequency technique, when displacement of the table is recorded. We expected that a study of the differences between the two force records would provide important information, because each instrument approached the problem from a different direction, and neither method seemed altogether free of error. Thus, if the records secured by each method closely agreed with one another, we would have strong evidence that the remaining errors were not important.

In addition, by testing large numbers of healthy persons and patients by both methods, we could not only compare and define their comparative utility in the

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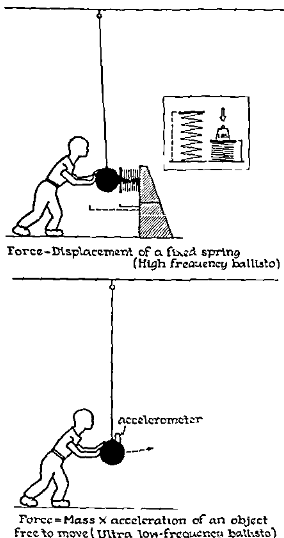


Fig. 1. Illustrations of the principles behind HF and ULF ballistocardiographs. Our problem is to measure the force with which the little man pushes on the ball suspended by a very long and light wire. In the first method we place a strong spring behind the ball. When the little man pushes the ball, this spring is compressed a short distance which we can measure (displacement measurement). Then, after turning the spring upright, we add weights until the spring is compressed the same distance. So we compare the unknown force with a known force. In the second method we leave the suspended ball as free to move as is possible. Now, when the little man pushes, the ball is accelerated. An instrument mounted on the ball records the amount of acceleration. The force applied can be calculated from the product of the *acceleration* recorded and the mass moved, i.e., the total mass of ball and accelerometer. Of course, the little man of this figure applies a force external to the ball, whereas the ballistocardiogram comes from forces having their origin within the body.

detection of cardiovascular abnormality, but also investigate the matter from a practical point of view, by asking the question, "Does ultralow-frequency ballistocardiography provide a better clinical method than the high-frequency technique?" Accordingly, during the past years we have tested over 400 patients and healthy persons by both methods; the second test was made as soon as the first was completed. An explanation of the differences between the records secured by the two instruments was sought by mathematical studies and by several series of experiments.

Theory

When one is interested in the forces, the theory behind the two types of ballistocardiographs can be easily grasped by reference to Fig. 1, which is designed to demonstrate the two different ways of measuring an unknown external force. In ballistocardiography, one is interested in the internal force, or what is proportional to such force, the acceleration of the body's center of gravity, and the same two methods can be used to detect it.

Instruments

The ultralow-frequency ballistocardiograph. The bed, made of a frame of hard aluminum alloy (61 ST 1) tubing, supporting a hammock of Grade A airplane fabric, was constructed for us by the late Dr. M. B. Rappaport, and was essentially similar to that which he has described.[6] After we had added a footplate, magnets, and fittings, the total weight was 3.3 kilograms. The general setup is shown in Fig. 2; the mass and physical properties are given in Table I.

Unlike that illustrated in Rappaport's article,[6] our bed was suspended from the ceiling by four wires, each 182 cm. in length. Because our room had a low ceiling, our bed—like Rappaport's instrument, and like Henderson's table of 50 years ago—is displaced laterally by a pair of pins (*AC*, Fig. 3), sharp at each end and 13.7 cm. long. When these pins are in place, the point of support of the suspension on this same side is not directly over the end of the pin (*A*), but over a point (*B*) 1.5 cm. from this base. The natural frequency of

Table I. Physical properties of our new HF and ULF tables, without a subject

	HF table	*ULF table*
Mass (Kg.)	36	3.3
Resonance frequency when loaded with 74-Kg. iron bars (cycles/sec.)	12.7	0.12
Damping (% of critical value)	5.0	10

Table II. Masses which move with the HF table, not including the subject

Table top and footplate	23 Kg.
Aluminum bracing	1
Picker Flexicast for shoulder yoke	10
Picker Flexicast for small of back	0.6
Nonslip pad	1.4
	36 Kg.

the system is about 0.12 cycles per second, a value which varies a little with differences in the stretch in the support wires caused by differences in the weights of the patients. No mechanism to provide additional damping has been used.

The electrical apparatus used is identical to that described by Rappaport, except that we use two bar magnets and two coils. The corresponding poles of the magnets are placed in opposite directions, so that the signal adds but the interference substracts. The resulting voltage is fed into circuits, described by Rappaport,[6] capable of integrating and differentiating it, but we have used only the differentiating circuit in this investigation. A record of acceleration was secured by means of the amplifier and recorder of a Sanborn Twin-Viso instrument. Up to this point, our equipment is only slightly modified from that described by Rappaport.

Because the coils are supported from the floor, we found it very difficult to get the record sufficiently free of building vibrations. After much experimentation we now use the following arrangement. Three small wooden pieces in contact with the floor support a 100-Kg. concrete block. Above this block is a wooden board the position of which can be adjusted by three screws. On this board lie a 15-cm. thickness of folded nylon blankets and another board on which the coils rest. This system renders our records almost altogether free of building vibration.

Of great value has been a secondary electrical circuit, with dry cells and a milliammeter, which indicates when one of the magnets touches the inside of its coil, an error of technique very likely to pass unnoticed without this warning device, and capable of causing marked distortion of the ballistocardiogram.

We use a calibrator designed by Dr. Walter Gamble.[16] Two forces, each of 140 Gm., one directed headward, the other footward, are allowed to act alternately on the table by a pendulum that interrupts first one and then the other.

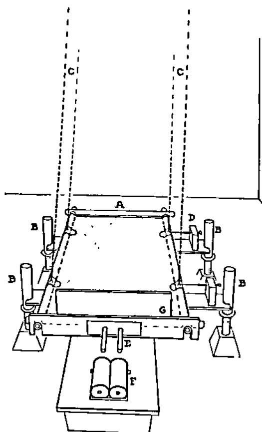


Fig. 2. Our ULF ballistocardiograph. *A*, The table. *B*, "Mine jacks," columns of heavy pipe extending between floor and ceiling to support the frame from which the table is suspended. Only the base is shown in the figure. *C*, Support wires. *D*, Lateral support. *F*, Coils shown withdrawn from magnets *E*. *G*, Footboard.

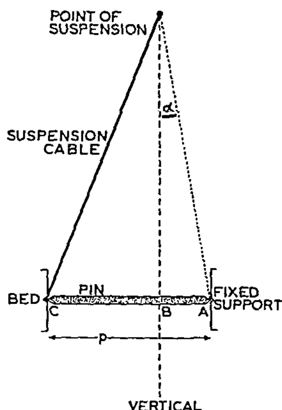


Fig. 3 Diagram which shows details of the suspension of our ULF instrument. To conserve space, the vertical dimension has been reduced in respect to the horizontal. AB = 1 5 cm.; angle α = 0.5 degrees.

This produces a series of square waves of about 0.4 second duration in the base line of the record. By this means the height of any wave of the ballistocardiogram can be related to the forces applied.

The newest high-frequency instrument. The design of our latest instrument stemmed from the desire to take ballistocardiograms with the subject tilted as well as horizontal. This instrument, made for us by the Technitrol Engineering Company, is shown and briefly described in Fig. 4. The masses and vibration properties are given in Tables I and II.

From the first, our standard technique of getting the subject tight on the table has been to have him lie on it with his feet in contact with the footplate and his knees bent. Then, by straightening his knees the body was forced headward, putting tension on the clothing and skin of his back as well as increasing the pressure of his heels on the footplate.

This technique has been improved as follows. A pad of thin rubber-like material, ordinarily used to prevent small rugs from slipping on a polished floor, has been placed on the table top; this has proved to be an important addition when the table

Table III. *Effect of tightening the subject on the HF table. The frequency and damping of movement between subject and table under various conditions*

Subject	*Conditions*	*Frequency (c.p.s.)*	*Damping, as defined by x_2/x_1*
J.U. (mass 85 Kg.)	Lying on nonslip pad, feet free of footplate	5 8	0 60
	On nonslip pad, feet against foot plate	8.1	0.52
	On nonslip pad, tight between Flexicast shoulder yoke and footplate	7 6	0 28
F.X.E. (mass 66 Kg.)	Lying on bare table, feet free of footplate	5 4	0.41
	Lying on nonslip pad, feet free of footplate	5 0	0.51
	Lying on nonslip pad, feet tight against footplate	7.1	0.35
	On pad, tight between Flexicast shoulder yoke and footplate	7 2	0.33
	Same, but tighter	8 2	0 68
B.P. (mass 72 Kg.)	On pad, tight between Flexicast shoulder yoke and footplate, tilted 15 degrees	7.2	0 34
	Same, level	7.0	0.72
	Same, Flexicast soft	6 8	0.52
	Lying loose on table, feet free of footplate	5.0	0.48

top is of polished metal as in our newer instruments. Also, we have used a patented device sold by the Picker X-ray Company under the name of *Flexicast*, and designed originally for the purpose of fixing various parts of the body for x-ray therapy. It is a kidney-shaped bag of rubber filled with a granular substance which is easily moulded at atmospheric pressure, but which, when air is pumped out of the bag, becomes stony hard. Two perforated aluminum tubes attached to the table footplate, and a movable crosspiece held in place by pins through each tube, serve to fix the Flexicast in position. For a while, we also used a small bag of Flexicast under the small of the back, but recently we have discarded it.

Therefore, in our latest technique the subject lies on the table on top of the nonslip pad with his feet on the footplate and his knees flexed. The Flexicast, while soft, is moulded around his neck and shoulders and held in place by the crosspiece adjusted to the length of the subject. The Flexicast is then hardened by connection to the vacuum line of the building. Then the subject, by straightening his knees, compresses himself between footplate and the shoulder yoke of the Flexicast.

By this technique the force of compression can be made as great as any subject can stand; we have used forces as high as 70 kilograms. But too much compression is painful; it also tends to arch the back and so may defeat its purpose of tightening the subject on the table by diminishing the area of contact. Also, anything which causes discomfort may defeat our purpose by altering the circulatory forces that we are measuring. Hence, we aim at the tightest attachment consistent with complete comfort and adjust the position of the crosspiece until this is obtained.

Theoretical comparison of the high-frequency and ultralow-frequency instruments. The physical properties of the two instruments are given in Table I.

One also needs to know the physical properties of the attachment of the subject's body to the tables. The latter data were found by experiments conducted on 3 healthy subjects as follows.

The table of the high-frequency instrument was clamped to the frame, and the subjects lay on it with a light bar strapped to their shins. A screen attached to this shin bar partly interrupted a light beam playing on a phototube; both light source and phototube were attached to the table.[7]

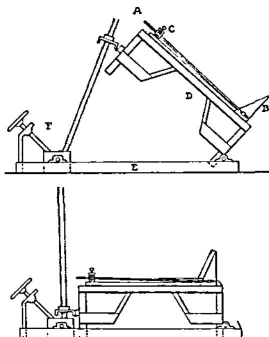


Fig. 4. Our newest HF ballistocardiograph, shown tilted, and in the horizontal position in which it is usually employed *A*, The table. Neither the 5-cm. suspension nor the strong restraining spring is shown. The table is made of 24 st aluminum, and with the footplate and bracing weighs 24 kilograms. *B*, The footplate. *C*, Movable crosspiece and pipes which attach it to footplate, used to support the shoulder yoke. *D*, Main table frame of cold rolled steel, weighing 110 kilograms. *E*, Base frame of cold rolled steel, also weighing 110 kilograms. *F*, The lifting mechanism, which weighs about 90 kilograms. Between base frame and floor are 4 pads of corrugated rubber and 2 of cork, each about 7 by 7 cm. and 7 mm. thick.

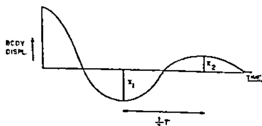


Fig. 5. Diagram of the movement of the body on a HF table, or on any other immobile surface, when a force applied headward or footward is suddenly released.

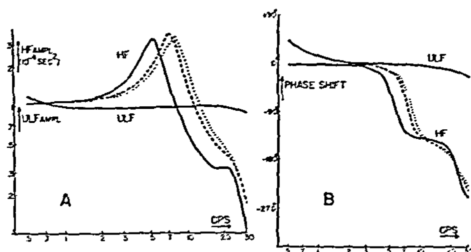


Fig 6. *A*, Amplitude characteristics of the HF and ULF ballistocardiographs. The former were calculated for various degrees of tightening of the subject to the HF table, using the top and bottom lines of Table IV. *Solid line:* Subject loose *Dashed line:* Subject tight. *Dotted line:* Subject very tight. The last is defined by a damping coefficient of 25 × 10⁶ Gm.sec.⁻¹ and a restoring force of 24 × 10⁷ Gm.sec.⁻² *B*, Phase characteristics for the same cases

Table IV. Average values and standard deviations for restoring force and damping as the 3 subjects were tightened on our HF table

Conditions	*Damping coefficient* (10^6 *Gm. sec.*$^{-1}$)	*Restoring force* (10^7 *Gm. sec.*$^{-2}$)
Loose, feet off footplate	11 ± 1	8.7 ± 1.0
Nonslip pad on table top, feet firm against footplate, back tightened by forcing it headward on nonslip pad	19	16
Nonslip pad on table top, Flexicast hardened to form shoulder yoke, body compressed between yoke and footplate	21	17
Nonslip pad on table top, hardened Flexicast supported by aluminum bracing, body compressed between yoke and footplate	18 ± 5	19 ± 2

The gain was reduced until the ballistocardiogram was scarcely visible; then the subject was given a push, either headward or footward, and suddenly released. The record after such release was that of a damped vibration, of the type shown in Fig. 5. Experiments of this type were conducted when the subjects were lying loose on the table and after various means had been taken to tighten them to it.

On the assumption that the body moves as a unit, the physical characteristics of the coupling between body and table can be calculated from the duration of the cycle and the ratio of the successive amplitudes, such as is shown in Fig. 5. The results are given in Table III.

In addition, from the data secured in Table III, from other data of the same type, and by making use of the constants and methods described,[5] we calculated the value for the damping and restoring force of the coupling between subject and table top. The average values secured for subjects lying loose on the table and after the application of various means of tightening them to it are given in Table IV. By our methods of tightening the subject the restoring force and damping are about doubled. The nonslip pad contributes a great deal to the success of the technique; without it the body slips badly on the polished metal of the table surface. The Flexicast yoke contributes something more,

but not very much, and its weight is a disadvantage.

The calculated amplitude and phase characteristics of the two instruments can be compared in Fig. 6.

Results

Comparison of the ULF and HF force records in healthy persons. Ballistocardiograms were taken by both instruments, each with a simultaneous electrocardiogram, on 30 healthy men and 20 healthy women, drawn from the faculty and students of the medical school, from personnel working in the hospital, and from a group of professional athletes who were soon to enter a long-distance swimming contest. The first test was made after the subjects had rested for 15 minutes or longer; they then walked about 20 steps to the other instrument, and the second test followed after another 15 minutes of rest. A calibration was made at the time each record was taken.

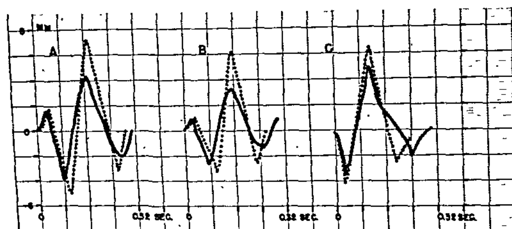


Fig 7. Average difference in timing and amplitude of recorded force between the general wave form and the ULF and HF ballistocardiograms of healthy young adults *A*, Comparison between average HF (*dotted line*) and ULF (*solid line*) ballistocardiograms of men. The time relationship between both curves was derived from simultaneously recorded electrocardiograms *B*, Same as *A*, for women. *C*, Difference between the force applied to the head of a cadaver (*solid line*) and the resulting HF ballistocardiogram (*dotted line*) (redrawn from a previous publication[1]) The data secured in this early experiment do not permit accurate placing of the two curves relative to one another in time, and they have been placed here with the I and J tips aligned in time If the dotted curve is placed a little later in time, the resemblance of *C* and *A* is even more striking. The calibration of the vertical coordinate: 10 mm = 280 Gm = 274 × 10³ dynes.

Table V. Averages of the differences found between the four main systolic waves of ULF and HF ballistocardiograms in 30 healthy men and 20 healthy women

	Differences in amplitude (mm.) (when 10 mm. = 280 Gm.)		*Differences in duration (sec.)*		*Differences in area (mm sec.)*	
	Mean	*σ*	*Mean*	*σ*	*Mean*	*σ*
H wave	−0 13	0 78	−0 0046	0 019	−0 003	0 03
I wave	+0 77*	1 18	+0 0065*	0 013	+0 040*	0 05
J wave	+2 48*	1 74	−0 035*	0 02	+0 033*	0 10
K wave	+1 25*	1 20	+0 029	0 03	+0.049*	0 09

A plus sign indicates that the HF value is larger. An asterisk indicates that the mean is significantly different from zero, for p = 0.05.



Fig. 8 Comparison of ULF and HF ballistocardiograms. A series arranged to show how similar the two types of records often are. The dots on the right margin indicate a calibration of 280 Gm. Note that the ULF calibration is usually larger than the HF one. ULF (*A*) and HF (*B*) records of T.P., a 25-year-old normal male medical student. *C* and *D*, Records of C.W., a 53-year-old woman with postural hypotension. *E* and *F*, Records of P.E., a 45-year-old woman with hyperthyroidism. *G* and *H*, Records of W.R., a 49-year-old man with hyperthyroidism and auricular fibrillation. *I* and *J*, Records of S.P., a 55-year-old woman with organic heart disease which was believed to be congenital in origin, possibly atrial septal defect. The reproduction is one half the size of the original records.

In the measurement of the records, typical large and small complexes of the respiratory cycle were selected; in each the amplitude of the H,I,J, and K waves from the base line of the record and the duration of each wave on this base line were measured. From the mean of the values obtained from the large and small complexes of the respiratory cycle of each subject, an average ballistocardiogram was constructed for that subject.

The measurements secured in the 30 men were used to construct a grand average normal male ballistocardiogram of the HF type, and another of the ULF type. Similar grand average normal female ballistocardiograms were also constructed. Knowledge of the time which elapsed between the tip of the R wave of the electrocardiogram and the peak of each wave of the HF and ULF ballistocardiograms permitted us to place the average HF and ULF records in the proper relation to one another in time. The time and amplitude relation of the two types of records are shown in quantitative terms in *A* and *B* of Fig. 7. It should be noted that, in the result obtained by this method of constructing grand averages, detailed information about small differences, such as notches and slurs, does not appear.

Table VI. *Comparison of HF and ULF records secured on the same person, in 250 patients*

	Per cent
HF and ULF have only their "usual" differences	60
ULF shows a notch which HF shows less clearly or not at all	25
ULF shows an I wave when I wave of HF is absent	2
Resonance in HF, none in ULF	1
Fine vibrations disturb ULF; not HF	5
Fine vibrations disturb HF; not ULF	2
Artifacts in ULF (coils touching magnets?)	3
Other differences	2

Table VII. *Comparison of the clinical interpretation given to HF and ULF records secured on the same person, in 250 patients*

	Per cent
Both records given the same interpretation	85
ULF suggests greater cardiac abnormality than HF	11
HF suggests greater cardiac abnormality than ULF	4

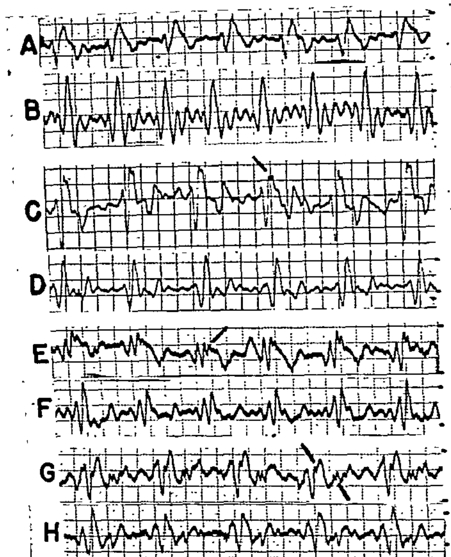


Fig. 9. Comparison of ULF and HF ballistocardiograms. A series arranged to show the common differences encountered in the two types of records. Lines point to features of interest. The ULF record is above the HF record of each subject. *A* and *B*, Records of J.H., 15 years old, complaining of nervousness; nothing else abnormal was discovered. Note striking difference between ULF and HF records. The form of the HF record indicates that the subject was not fastened tightly to the instrument and there has been an error in technique *C* and *D*, Records of J.H., a normal 23-year-old man. Note notching of the tip of the J wave in the ULF, but not in the HF record. Note other notches in ULF record not seen in HF record *E* and *F*, Records of K.E., a healthy 54-year-old man. Blood pressure of 125/85 mm. Hg Note the flat, deeply notched J wave of the ULF record which looks abnormal, whereas the HF record looks altogether normal. Note also that notches of the same frequency as that of the J wave are to be seen in other places in the ULF record. *G* and *H*, Records of I. H., a normal 41-year-old man. Blood pressure of 120/80 mm. Hg. Note the notch in the I-J segment of the ULF record not shown in the HF record. Note also notches of similar frequency in the L-M-N complex of the ULF record. These notches do not appear in the HF record. The reproduction is four fifths the size of the original records.

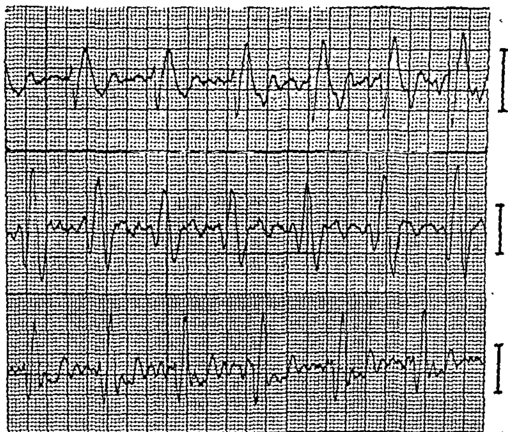


Fig. 10. Experimental ULF (*top*) and HF ballistocardiograms (subject loose, *middle;* subject tight, *bottom*) of Subject B P. The vertical lines in the right margin show a calibration of 274 × 10³ dynes. The reproduction is the size of the original.

The results of the statistical analysis, made by the method of paired experiments, are given in Table V. The H waves of the two records are essentially identical in height and area; the I wave of the HF record tends to be a little deeper (t = 4.1) and a barely detectable amount broader (t = 3.1) than that of the ULF record; the average J wave of the HF record is much taller (t = 8.8) and much narrower (t = 11.2) than that of the ULF record. Despite this difference in shape the average J-wave areas are so very nearly similar in the two types of records that the significance of the difference was just demonstrated, t = 2.2. The amplitude and area of the K wave are significantly larger in the HF records.

The tips of the H and I waves of the HF records follow those of the ULF records by an average of 0.012 and 0.022 second, respectively, and these are significant differences. The average differences between the timing of the tips of the J and K waves are still smaller and not statistically significant in our small series.

Comparison of ULF and HF records secured in patients with and without cardiovascular disease. The experience with patients is summarized in Figs. 8 and 9 and Tables VI and VII. Thus, Fig. 8 is designed to illustrate the many instances in which ULF and HF records resemble each other closely. In contrast, Fig. 9 illustrates the differences most commonly encountered. In Table VI, the experience with the two types of records is compared. In Table VII, the senior author has compared his interpretation of the two records in terms of cardiac function.

The differences which are found between HF and ULF records taken on the same patient can be classified into three groups. In the first group are the differences in size and shape of the waves. Thus, in the patients, as in the healthy persons, the J

wave of ULF records tends to be shorter and broader than that of HF records. Also the ULF K wave is usually shorter than that of the HF record.

The differences of the second group manifest themselves as notches, divided waves, and slurs. Examples of these can be clearly seen in Fig. 9. Almost without exception these extra waves are seen in the ULF record, and they are absent or less well shown by the HF record.

The differences of the third group are more diverse for they comprise all those not included in the first two groups. Some are most certainly due to artifacts from building vibrations, to which both instruments are subject at times, whereas others appear to be artifacts from contact between the moving table and some stationary object. Occasionally, an unexplained difference is found between the two records, and one must recall that the diseased heart is more variable in its performance from minute to minute than is the normal heart, and that our HF and ULF records were not taken simultaneously but about 20 minutes apart. Thus, the differences in this diverse third group are due chiefly to the common accidents and artifacts that occur in taking ballistocardiograms; they will not be discussed further.

Analysis of the differences between the two force records. We first asked ourselves whether differences in the physical properties of the two setups would explain the differences found between their records. If this were true, we should be able to start with the record secured by one instrument and, through the use of physical principles, compute the record of the other. The mathematics involved in such a computation, although complex, have long been known, but until recently such work has been so laborious that the practical application of these methods to a problem such as this has been impossible. It became possible only recently with the development of the digital computer. Accordingly, the problem was attacked by means of a Fourier analysis of the records of 2 healthy subjects (B.P. and F.Y.E.), using the Univac computer at the University of Pennsylvania.

We took as a starting point a typical complex secured by the low-frequency instrument, a complex midway between the largest and smallest ones of the respiratory cycle. The complex chosen for

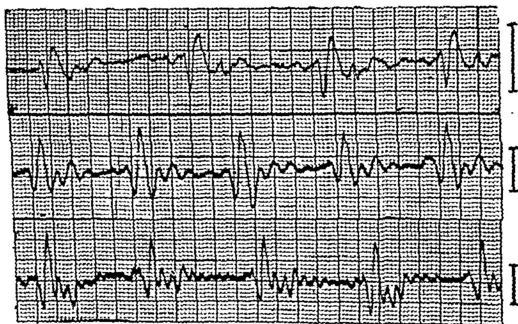


Fig. 11. Experimental ULF (*top*) and HF ballistocardiograms (subject loose, *middle*, subject tight, *bottom*) of Subject F.Y.E. Calibration of 274 × 10³ dynes is indicated in the right margin. The reproduction is the size of the original.

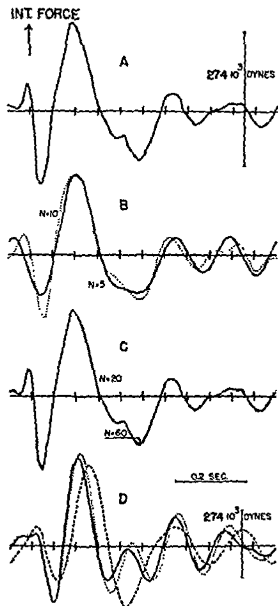


Fig. 12. *A*, Enlarged experimental ULF ballistocardiograms (Subject B.P.). *B*, Synthesis of this ballistocardiogram using the first 5 and 10 Fourier harmonics. *C*, For the first 20 and all 60 harmonics. *D*, HF ballistocardiograms calculated from the curve in *A* for 3 degrees of tightening given in Fig. 6. (Subject loose, *dashed line;* tight, *dotted line;* very tight, *solid line.*) All curves are synchronous. The same calibration is valid for *A*, *B*, and *C*. Note the improvement in similarity in *A* and *D* with increasing tightness of the coupling between the subject and table.

each subject (the third complex in the top row of Figs. 10 and 11, respectively) was enlarged photographically as is shown in Figs. 12,*A* and 13,*A*. After measurement, each of these curves was developed into a Fourier series of 60 harmonics, i.e., 60 sine waves, that with the lowest frequency having the frequency indicated by the heart rate of the subject. For both ultralow-frequency ballistocardiograms the amplitude of the lower, middle, and higher harmonics is given in Fig. 14. Our findings resemble but are not exactly similar to those of Honig and von Wittern,[8] for we did not find a second peak around 10 c.p.s. as high as that found by these authors.

Obviously, the lower harmonics constitute the major part of the ballistocardiograms, as is demonstrated in Figs. 12,*B* and 13,*B*, and are responsible for the general form and amplitude of the waves. The higher frequencies play a part only where notches and slurs are concerned (Figs. 12,*C* and 13,*C*).

To construct a theoretical high-frequency ballistocardiogram from measurements made on the ultralow-frequency record the computation was continued as follows. Each of the 60 harmonics was shifted in time and changed in amplitude according to information about the properties of the HF systems given in Fig. 6. Thus, those harmonics of the ULF record which were delivered in resonance with the movement of the body on the table were increased in amplitude, those harmonics of the ULF record higher than the resonance frequency of the body on the table were reduced, and each was shifted in time in accord with the phase shift of the system. Finally, a new curve was constructed by again adding the altered components at each instant of time. Similar theoretical curves were constructed for several degrees of tightness of attachment of the subject to the HF tables.

The results (Figs. 12,*D* and 13,*D*) show clearly that the curves thus constructed from measurements made on low-frequency ballistocardiograms bear a close resemblance in shape and amplitude to the HF ballistocardiograms (Figs. 10 and 11) secured experimentally on the same subjects. Obviously, therefore, we have a clear understanding of the reason for the major points of difference between the two types of records,[9] the average differences of wave height and timing shown in Fig. 7,*A* and *B*.

However, for reasons to be discussed,

we were not so confident that the notching of the waves seen in the ULF, but not in the HF records could be explained completely by differences in physical properties of the two instruments, although it was clear from the computation that the higher frequency components of the ballistocardiogram were strongly attenuated by the HF instrument (Fig. 6,*A*), so that the effect of high-frequency forces, notching of the waves, would be reduced in HF records. Before accepting this view completely, we sought to discover whether differences in movements of the body in space, so obvious to anyone who has taken

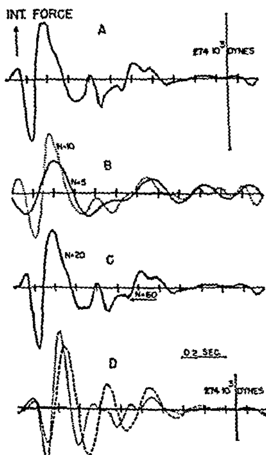


Fig. 13 *A*, Enlarged experimental ULF ballistocardiogram (Subject F.Y.E.) *B*, Synthesis of this ballistocardiogram using the first 5 and 10 Fourier harmonics *C*, For the first 20 and all 60 harmonics. *D*, HF ballistocardiograms calculated from the curve in *A* for 2 of the 3 degrees of tightening given in Fig. 6 (subject loose, *dashed line*; tight, *dotted line*). All curves are synchronous. The same calibration is valid for *A*, *B*, and *C*.

both types of records, might not be playing a part.

Is there an error from "loose parts" moving in the body? HF and ULF records are not taken under identical conditions. When a subject is on the ULF table, the movement of the body in space is plainly visible; but when he is lying on the HF table, no movement can be seen by the naked eye. As measured by a microscope that is supported from the floor, the distance which the body moves during the respiratory cycle may be 100 times greater on the ULF than on the HF instrument. The systolic displacement of a pointer attached to the shin bar of a subject lying on the ULF instrument is about 5 times as great as that of the same subject lying on the HF instrument, a value which agrees with that calculated from theory. Not only does the amplitude of the systolic movement differ, but also the shape; the body's displacement when on the HF table has the pattern of the second time derivative of the body's displacement when on the ULF bed.

The body is not a solid block.[19] The limbs and head move on the trunk, and many abdominal organs move with respiration. Collections of fluid are present normally in the circulation, cerebrospinal canal, gastrointestinal tract, and bladder; abnormally, they often appear in the pleura and peritoneum. If the body frame is suddenly moved forward in space, the pools of fluid and the loosely connected body parts, left behind initially because of their inertia, will be accelerated as their connections tighten; and these masses, again because of their inertia, will continue to move forward, decelerating, for a brief period after the body frame has stopped. Also, waves within the fluid masses may persist after body movement has ceased. Such movements within the body may cause trouble to one attempting to interpret the ballistocardiogram: (1) by producing secondary inertial forces which warp the record of the forces of the circulation, and (2) by interfering with the correct estimation of the circulatory forces from the product of acceleration and body mass, because the total mass, as determined by a balance, will undoubtedly be greater than the mass mo[illegible] [illegible]on ac-

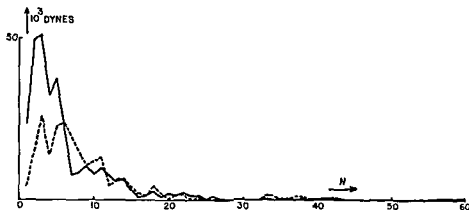


Fig. 14. The amplitude of the Fourier components of the ULF ballistocardiograms represented in Fig. 12,A (*solid line*) and Fig. 13,A (*dashed line*).

celeration of the body frame began, if loose masses are left behind until their connections tighten. Obviously, we needed to convince ourselves that there was not a serious source of error here; hence, more knowledge both of the presence of "loose masses" and of the character of their connections was sought.

The effect of introducing a loosely connected mass. An iron block of either 5 or 10-kilogram mass was placed on the body of 6 subjects who lay first on the HF and then on the ULF ballistocardiograph. The frequency of the block-body coupling was determined by striking the block.

The results (Figs. 15 and 16) were consistent. When the subject lay on the ULF instrument, the presence of the block distorted the record by producing notches on the waves and, sometimes, changing the height of the peaks of the waves. The position of the abnormal notches on the normal waves of the ballistocardiogram varies with the frequency of the block-body coupling.

But when the subject lay on the HF instrument, the presence of the same block either had no effect on the record at all or caused only a slight slurring. Obviously, loose parts attached to the body of a subject whose control ULF record shows no notches give rise to notches which resemble those seen in the ULF records of certain other subjects. The question immediately arises whether there are loose parts in the bodies of certain people which, by wobbling like the iron block when the body moves in space, produce secondary forces which distort the ULF ballistocardiograms with artifacts not related to the circulation.

We designed an experiment to answer this question. If loose parts capable of causing distortion in ballistocardiograms were present, we could demonstrate them by first applying to a subject on the ULF ballistocardiograph a force sufficient to set his body in motion, and then having that force terminate instantaneously. The continued appearance of forces in the record after the inciting force had ceased would indicate the presence of secondary forces which could be attributed to loose parts of the body which were still moving with respect to the body frame.

First, we demonstrated that, with iron blocks instead of a subject on the ULF ballistocardiograph, forces induced by tapping or by pulling on a thread until it broke did terminate almost instantly, an experiment which also indicates that there is no important source of interfering high-frequency vibrations in the table itself. Then, with a patient on the ULF instrument, the amplification was cut down until the ballistocardiogram was just visible, and similar forces were applied to the subject's body. In 200 experiments on 30 subjects the transient force was applied by tapping the head or the feet. In 30 other experiments on 6 subjects a thread was tied about the subject's neck or feet and given a jerk so sharp that it broke. In these latter experiments, rupture of the thread often produced a burst of high-frequency vibrations which, also present

when the experiment was performed with iron bars instead of a subject, were plainly artifacts connected with the breaking of the thread and not due to the movements of parts of the body. Otherwise, the results secured in the two series were very similar, and typical examples are shown in Fig. 17.

Two features are seen in almost every record: first, a slow component returns the record to the base line, 0.08 to 0.12 second after the peak of the transient; and second, superimposed on this slow component are more rapid vibrations, not in a single frequency in any subject but which, when measured roughly, ranged from 10 to 20 cycles per second in different subjects. Occasionally, as in *A* and *D* of Fig. 17, one of these components is present without the other. Whatever the combination the effect is very brief, usually over in about 0.2 second.

Thus, through the use of inciting forces many times larger than those which are the genesis of ballistocardiograms, we have demonstrated small secondary forces of brief duration which cannot be attributed to the circulation. If the much smaller inciting forces which are the genesis of the ballistocardiogram brought out secondary forces proportionate in size, these noncirculatory forces could have an influence on the ULF record, and the production of notches would be the most obvious effect. Thus, studies of the same problem from the theoretical viewpoint also seemed to be worth while, although one could hope to explore only a few of the many possibilities.

Theoretical studies on the effect of loose masses within the body. In order to get a better quantitative appreciation of the influence of a loosely coupled mass on the recorded ballistocardiogram, a number of cases were worked out quantitatively, making use of the digital computer of the University of Utrecht and of a suitable analogue computer. Since little knowledge is available in regard to the numerical values that should be assumed in these calculations, a fairly wide range was chosen, namely: (a) for the "loose" mass: 2,4,8, and 16 Kg.; (b) for its coupling to the remainder of the body: a resonance frequency of 5, 10, and 20 c.p.s.; (c) for its damping: 40 and 100 per cent of the critical value.

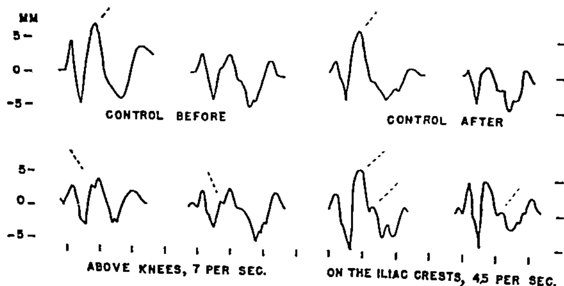


Fig. 15. Effect on the ULF ballistocardiogram of the experimental introduction of a "loose" mass. Drawings of typical large and small complexes of the respiratory cycle of the record of a healthy young man. *Upper left:* Control record before the experiment. *Lower left:* Record after the introduction of a 10-Kg. iron block placed on the skin above the knees, where it had a coupling with the body whose frequency was 7/sec. *Lower right:* Record after the block had been removed to the lower abdomen, where it rested on the skin over the iliac crests Here the frequency of its coupling was 4 5/sec. *Upper right:* Control record after removal of the block. Note the appearance of notches after the introduction of the "loose" mass. The position of these notches on the record changes when the frequency of the block-body coupling changes.



Fig. 16. Effect on the ballistocardiogram of the movement of a "loose" mass: a 10-Kg. iron block lying on the subject. *Top:* Control ULF ballistocardiogram of a normal subject. *Second:* Same subject, with block placed above his knees. Frequency of block-body coupling 5/sec. Note the notching of the ULF record which results. *Third:* HF ballistocardiogram of the same subject. *Bottom:* Same subject with the same block placed above his knees. Frequency of coupling 5/sec. No notching of the HF record results.

Each combination of three figures, one being taken for each heading, defines a specific problem. For a great number of combinations, frequency characteristics (both amplitude and phase) were computed by Miss van Hoorn[11] for the HF and ULF instruments described in this paper. A few of the results are reproduced as Figs. 18 and 19.*

Discussion

In the theory of the ballistocardiogram, four situations have been envisioned: in the first approximation the body is considered to be a solid unit with its support[5]; in the second, the body is considered to be a solid block with contact with its support through a viscoelastic coupling[3,6,7]; in the third, we envision the circulatory system as distinct from the body frame and connected to it by a viscoelastic coupling; and in the fourth, we regard the frame as divided into two or more parts, each connected with its support.[3,12] A still closer approximation of reality would be a combination of the last two. The first three approximations have been considered before; the second and fourth are treated in this paper (Figs. 6 and 18).

Problems concerned with the attachment of the parts of the body to one another have seldom come up in medicine or physiology, but they were studied by Wilson, Cunningham and Griswold,[10] who shook the body at various frequencies and concluded that it did not move as a unit. If the parts of the body were free to move within the limits imposed by elastic couplings of known properties, one could calculate the effect we seek. But there is doubt whether one can safely assume that these properties are linear. Thus, the liver moves a centimeter or two during each respiration, and its attachment to the body frame is not solely through the ligaments which limit its motion, but, also, when the patient is recumbent, through the friction of its weight pressing against the spine and ribs. If the force required to overcome this friction is not linear, the motion imparted to the liver by movement of the body frame in space cannot, at present, be calculated with confidence. But one could demonstrate it by experi-

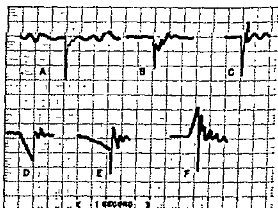


Fig. 17. Forces registered in ULF records after a transient force has been applied and withdrawn as rapidly as possible. *Top row:* Typical examples of records secured after the subject was tapped on the head. *Bottom row:* Typical examples of records obtained when a thread attached around the chest, neck, or feet was pulled until it broke. Note the secondary vibrations set up and the slow return to the base line often seen. The record was attenuated until the ballistocardiogram was hardly detectable.

*A full account of the results may be obtained by writing to the Department of Medical Physics, Physics Laboratory, Bylhouwerstraat 6, Utrecht, referring to Internal Report V 1682. A mimeographed copy of the full report is available on request.

ment, and our results indicate that even when the experimental inciting forces are many times larger than those which occur naturally during the taking of the ballistocardiograms, the secondary forces called forth are small. So, despite our doubts, the results of our experiments and of our calculations agree with each other, and with the results secured by Wilson, Cunningham and Griswold[10] when the body was shaken. One must conclude that movement of loose parts of the body and in the fluid pools has little effect on the ballistocardiogram. But this does not mean that such effects are negligible.

From our theoretical studies, one can draw four conclusions. (a) The HF force tracing is distorted by movement of the body on the table, although it should be noted that because of recent improvements this movement is much smaller and the distortion caused is much less than that sometimes seen on records secured by older instruments with high natural frequency. (b) The HF force tracing is little affected by the presence of "loose" masses connected with the body. (c) The ULF force tracing is distorted very little by motion between the body and its support. (d) Since the ULF acceleration tracing also represents the higher frequency components, it is sensitive to effects caused by the relative motion of parts of the body. Notching of the curve might be enhanced by this property.

From the calculations and the results of the experiments it is evident that records taken with the ULF instruments provide high-frequency information of a type which is absent in the HF record, and we are confronted with the question of the physiologic origin and the clinical value of this new information. It is far from certain that all the slurs and notches so commonly seen in ULF ballistocardiograms have their origin in the circulation, and, if not, a better estimate of circulatory abnormalities might be made if they were not recorded.

The chief argument in favor of a circulatory origin for the notches so often seen in ULF record lies in their apparent movement with respiration. Thus, if located in the H-I or I-J segment, such notches commonly move up and down the segment with the phases of respiration. This movement suggests a physiologic origin secondary to differences in the strength of cardiac contraction caused by the differences in cardiac filling which follow the changing filling pressures of the respiratory cycle.

Thus, such notches have been interpreted as indicating asynchronism of the forces of the two sides of the heart.[15] This is a reasonable explanation supported by other physiologic evidence. Indeed, notches on the J wave have been produced experimentally by simulating asynchronous cardiac ejection in cadavers.[11] But several observations provide an alternative explanation, although they certainly do not disprove this physiologic interpretation. First, careful measurement shows that in many instances the notches, when moving up and down with the respiratory cycle, maintain their position in time; it is changes in the slope of the segments which make them move toward or away from the base line. Second, when the introduction of a loosely coupled mass produces notches in the ULF record which are clearly not due to the circulation, these notches also appear to move with respiration. Evidently, the fact that a notch changes position with respiration is not proof of its circulatory origin. Third, when one sees systolic notching in the ULF record, as in *C*, *E*, and *G* of Fig. 9, careful inspection sometimes discloses similar high-frequency phenomena in the diastolic parts as well. Some notches occur so late in diastole that they are unlikely to have a cardiac origin, and when such notches are associated with systolic notches, one suspects that both may have a similar origin outside the circulation.

We have carefully searched the clinical data to see whether those subjects with systolic notches in the ULF record, but not in the HF record, showed any clinical similarities which would aid in interpreting the finding. But we have not yet found any. Systolic notching occurs in the ULF records of many young adults who appear to be in good health. If such notches are evidence of cardiac abnormality, it is of a new type which occurs frequently in apparently healthy persons, and which is not necessarily related to any of the

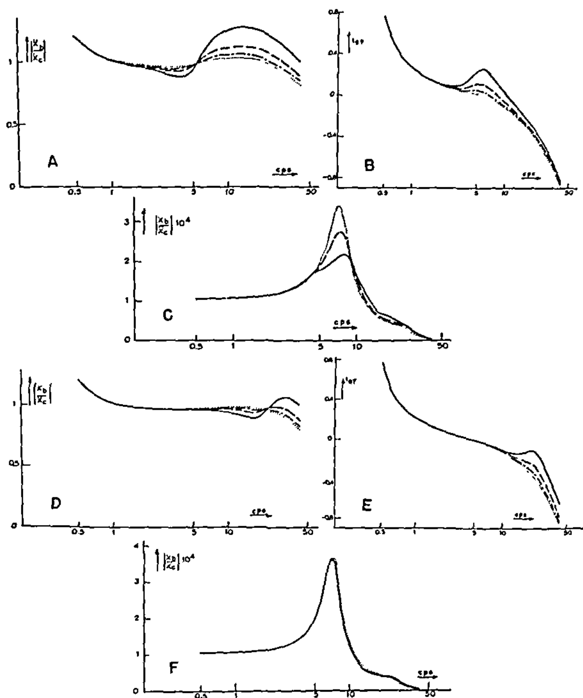


Fig. *18*. *A*, Amplitude characteristics of the ULF instrument, taking into account the coupling between body and support, and that between the body and a loose part of it, of (a) 2 Kg. (*dotted line*), (b) 4 Kg. (*dashed-dot line*), (c) 8 Kg. (*dashed line*), and (d) 16 Kg. (*solid line*). The natural frequency of the loose part is taken as 5 c.p.s., and its damping is 40 per cent of the critical value. *B*, Phase characteristics for the same cases. *C*, Amplitude characteristics of the HF instrument for cases a, c, and d in *A*. *D* and *E*, Same as *A* and *B*, except that the natural frequency of the loose mass is 20 instead of 5 c.p.s. *F*, Same as *C*, except that the natural frequency of the loose mass is 20 instead of 5 c.p.s. (cases a and d only). The amplitude of the internal acceleration of the center of gravity is denoted $\ddot{x}_i$, the amplitude of the acceleration of the ULF instrument is $\ddot{x}_b$, that of the displacement of the HF instrument is x_b. The phase angle between drive and response is φ.

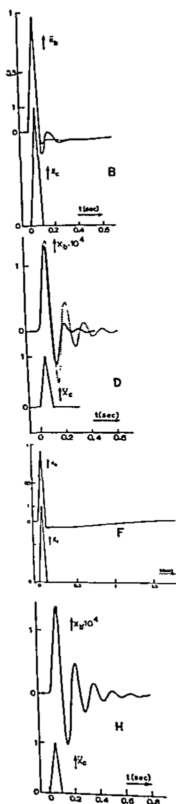


Fig. 19. (For legend see opposite column.)

types of heart disease with which we are familiar. In contrast, abnormalities in the low-frequency phenomena shown by the Fourier analysis to be the dominant components of ballistocardiograms, and recorded by both HF and ULF instruments, are readily related to cardiac disease as we know it from other sources, and to the effect of treatment upon it. While the search should certainly be continued, we have as yet found no evidence that important clinical information is contained in the notches and slurs recorded solely by the ULF instruments.

Similarities of HF and ULF records. By spending so much time and effort in an attempt to understand the differences found between the two types of ballistocardiograms, we run the risk of exaggerating their importance in the reader's mind. For most practical purposes these differences are of little moment. Of far greater importance is the finding that the ULF and HF methods, which are quite different methods of detecting forces, are in good quantitative agreement about so many aspects of the forces of the circulation. The agreement in contour, depth, and duration of the H and I waves of the two types of records is so close that for practical purposes the results are identical. In our early HF records the terminal complex (the L,M, and N waves) was often overwhelmed by aftervibrations, but with the recent improvements it usually appears as clearly as it does in ULF records. All this is strong evidence that we are getting a reasonably true record of the forces of the circulation by both methods. The sole important difference lies in the J wave, which, although of nearly similar area in the two records, is consistently taller and narrower in HF records. If one bases his judgment on

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Fig. 19. Response of the ULF instruments to a triangular shaped internal acceleration of the center of gravity x_c (proportional to internal force) (*bottom in B, D, F, and H*) *B,* (*top*) The acceleration $\ddot{x}_b$ of the ULF instrument for cases a and d of Fig. 18,*A* and *B*. *D,* (*top*) The displacement x_b of the HF instrument for the same cases *F,* (*top*) The acceleration $\ddot{x}_b$ of the ULF instrument for cases a and d of Fig. 18,*D* and *E*. *H,* (*top*) The displacement x_b of the HF instrument for the same cases.

area rather than altitude of the wave, the two methods give almost identical results.

The finding of striking similarity between corresponding wave *areas* in the two methods is again in agreement with theoretical considerations, for the physical properties of the two systems indicate that there is little distortion in the lower frequency harmonics of either system. Therefore, records of the velocity of the body's center of gravity taken by the two instruments will be more similar than records of its acceleration, the subject of this study. For the same reason, records of the displacement of the body's center of gravity, the second integral of the HF records described in this paper, and the ULF records when displacement is recorded would be almost identical. It is in the lower harmonics that the important clinical information has been identified.

Chiefly because of the difference in J-wave amplitude, the over-all amplitude—the vertical distance between the tips of the I and J waves—is larger in HF than in ULF records. This difference in amplitude is very constant; in 50 consecutive subjects tested by both methods the correlation between the two amplitudes was very strong, $r = 0.87$. The test-retest correlation for 53 subjects tested on our original HF instrument was 0.91,[14] an almost identical value. Therefore, arrangement of the subjects in the order of the amplitude of their HF or ULF records would yield two series not significantly different in arrangement, and, although the normal standards for amplitude would be different in absolute value, patients with abnormal amplitudes could be as readily detected by one method as by the other.

Which is the better method? No simple answer can be given to this question. The ULF is a beautiful method, and its chief advantage is obvious, i.e., movement between body and table is avoided. By our present setup we can secure records of the displacement and velocity of the body's center of gravity as well as the force record discussed in this paper. On the other hand, the apparatus is at present fixed in position in one room, and it is more fragile than the HF table. Technicians find it more difficult to calibrate and to operate. Acute experiments on subjects are more difficult to perform on the ULF instrument; unless care is taken, tension in tubes and wires attached to the subject may restrict the movement of the table.

In contrast, the HF instrument is so strongly constructed that breakage and mechanical difficulties almost never occur. The subjects must be carefully made tight on the table, and there is a source of error inherent in this, since differences in the degree of tightness cause small differences in the record. But even when the subjects are maximally tight, the HF record will not show high-frequency phenomena as does the ULF record. The HF instrument requires a larger amplifier than does the ULF instrument. Although the electronic equipment in use at present permits only the force record, its integrals could be readily secured by additional equipment. Our routine HF force calibration is both easier and more accurate than the best we have been able to obtain on the ULF instrument. Our most recent instrument permits records with the subject tilted as well as prone, a great advantage in the study of dyspneic patients who cannot lie flat. Experiments are easily performed on subjects lying on the HF table; the attachment of tubes and wires to the subject, and the disturbance of taking blood pressure by the auscultatory method make no difference at all. As an instrument for routine clinical testing to be run by hospital technicians the practical advantages of the HF over the present ULF system are still considerable.

If high-frequency phenomena over 10 per second prove to be of importance in the diagnosis of cardiac disease, or in the estimation of the effects of therapy, the ULF instrument will be the only one to use. But it must be pointed out that this prolonged clinical study has produced no evidence that important clinical information lies solely in the range in which the ULF record is clearly superior.

Conclusion

An improved form of high-frequency ballistocardiograph, which can be tilted, is described. A new ultralow-frequency ballistocardiograph is also described.

A large series of patients and healthy persons has been tested on both instruments. There are two main differences between the records of the cardiac and circulatory forces obtained by the two instruments: (1) most large waves of the HF records are taller and narrower than those of the ULF records; (2) notches and slurs often appear in the ULF records which have no counterpart in HF records.

By a mathematical analysis of the physical properties of the two instruments, and by some assumptions in regard to the physical properties of the connections of various parts of the body, these differences could be accounted for theoretically.

The apparatus required for the HF method is more rugged and simpler to use than that of the ULF method, but the movement of the subject on the table is a serious drawback. This drawback has been reduced by modern techniques, but the difficulty has not been altogether mastered.

The ULF method, although somewhat more difficult for technicians to calibrate and operate, avoids the difficulty due to movement between subject and table. But, since all parts of the body are not tightly connected with one another, this record is more subject to distortion from secondary inertial forces which arise from relative movement of parts of the body and in fluid pools within it. This difficulty does not seem to produce more than a minor effect on this record in the situations which we have examined.

Judged from the physical properties of the two systems, HF and ULF records of the velocity of the movement of the body's center of gravity, the integrals of the records described here, would be more similar than their force records. For the same reason, HF and ULF records of displacement of the body's center of gravity, the second integrals of the records described here, would be almost identical.

The similarities of the two force records are much more striking than the differences. The terminal complexes are well shown by both methods. The gross abnormalities in form and amplitude, on which clinicians should rely for the detection of cardiac or circulatory abnormality, are clearly shown by both methods.

The major part of the work was conducted when the authors worked together in Philadelphia, but many of the calculations were completed by the junior author after he had returned to Utrecht. We are greatly indebted to Miss Willy van Hoorn, who played an important part in the calculations made in Utrecht, and to Dr. A. van der Sluis, who assisted in the operation of the "Zebra" digital computer of the University of Utrecht. We are also indebted to Mrs. Gertrude Noordergraaf for technical assistance in taking and evaluating the ballistocardiograms made on patients and healthy persons in Philadelphia, and to Mrs. Maxine Rockoff, who wrote the program to handle the data given to the Univac digital computer of the University of Pennsylvania.

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Evaluation of the pressure time derivative method for estimating peak blood flow

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The ability to measure the instantaneous blood velocity or flow in the human vascular system is of major importance in the study of cardiovascular dynamics in health and disease. At the present time, one of the more promising approaches to the measurement of aortic blood velocity in intact man is the pressure gradient technique.[1] This method is based on the Navier-Stokes equations which relate the axial aortic pressure gradient to the instantaneous blood velocity. After considerable simplification the following equation was derived:

$$\frac{-\delta p}{\delta z} = \rho \frac{\delta w}{\delta t} + aw \qquad (1)$$

where p is pressure, z is the axial coordinate of the vessel, ρ is the blood density, w is the blood velocity, t is time, and "a" is a "velocity resistance coefficient." Thus, Equation 1 states that the instantaneous spatial rate of change of pressure along the axis of a blood vessel, $-\frac{\delta p}{\delta z}$ consists of two components, an inertial component, $\rho\frac{\delta w}{\delta t}$, and a frictional component, aw. If the pressure gradient, $-\frac{\delta p}{\delta z}$, can be measured, and if ρ and "a" are known, then Equation 1 may be continuously solved for w, the instantaneous blood velocity, by means of electrical analogue techniques.[1]

Although this method has been employed in the experimental animal[2] and in man,[3] its application is limited by the technical difficulty in obtaining a valid pressure gradient. To circumvent this problem a further simplification of Equation 1 is theoretically possible.[4-9] If it is assumed that the pulse pressure wave travels down the aorta undistorted and unattenuated, and that there are no reflected waves, then it can be shown that the following relationship is true:

$$\frac{-\delta p}{\delta z} = \frac{1}{c}\frac{\delta p}{\delta t} \qquad (2)$$

where $-\frac{\delta p}{\delta z}$ is the instantaneous pressure gradient, $\frac{\delta p}{\delta t}$ is the first time derivative of pressure, and c is the pulse wave velocity. These assumptions are only approximately correct. Nevertheless, to the extent that they are true, $\frac{1}{c}\frac{\delta p}{\delta t}$ may then be used instead of $-\frac{\delta p}{\delta z}$ to compute the velocity, w,

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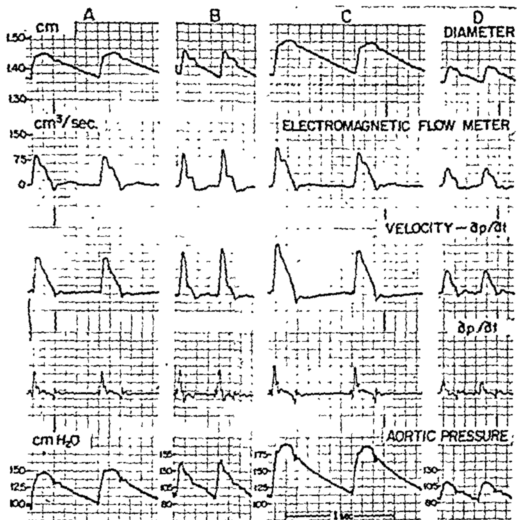


Fig. 1. *From the top downward:* Diameter of the aorta, EMF flow, $\delta p/\delta t$ velocity, $\delta p/\delta t$, and the pressure pulse are illustrated. *A*, Curves obtained during the control period. *B*, After administration of isoproterenol. *C*, During anoxia. *D*, After acute hemorrhage. The similarity between the EMF flow and the pressure time derivative method ($\delta p/\delta t$ velocity) can be seen; however, it should be noted that these curves were among the better ones obtained. The $\delta p/\delta t$ signal was passed through a low-pass filter before recording.

in an analogue computer. The $\frac{\delta p}{\delta t}$ may be more simply and accurately obtained than $-\frac{\delta p}{\delta z}$. Therefore, one could take advantage of this pressure time derivative method, provided that it can be shown to be valid experimentally in spite of the foregoing broad assumptions.

Recently, Jones and associates[6] examined part of this problem experimentally and found excellent correlation between stroke volume estimated by the dye-dilution technique and that by this pressure time derivative method. In their study, changes in diameter of the vessel associated with changes in pressure were ignored. Since the measurement of instantaneous blood velocity plays an important role in the study of circulatory dynamics, it would be useful to establish the validity with which the pressure time derivative method estimates instantaneous values. The Kolin electromagnetic flowmeter (EMF) has been shown to be adequate to estimate instantaneous blood flow in the aorta.[10-12] It is not possible to monitor flow at the point of measurement of pressure since the vessel is splinted

by the application of the flowmeter probe. However, it is possible to monitor flow at some point either upstream or downstream from the point of measurement of pressure. Under these circumstances the instantaneous flow at the monitoring probe and at the pressure measuring point will be different. Nevertheless, one might expect relatively good correlation of the peak-to-nadir values of flow by the two methods if the hydraulic capacitance of the intervening blood vessel is not large.

In accordance with the foregoing considerations, experiments were carried out for the purpose of comparing the peak-to-nadir values of blood flow obtained with a Kolin EMF to those obtained by the pressure time derivative method.

Methods

Ten mongrel dogs were studied; these weighed between 15 and 20 kilograms and were anesthetized with a morphine-chloralose mixture. The descending thoracic aorta was exposed and the animal was maintained on a respiratory pump. The EMF probe (30 to 40 mm. in circumference) was placed around the descending thoracic aorta just below the junction of the left subclavian artery, after minimal removal of the aortic adventitia. The EMF was calibrated with saline immediately prior to each experiment by passing a known flow through the EMF probe, and recording the corresponding electrical signal. Instantaneous aortic diameter was measured by a pair of recording calipers sewn to the aortic wall approximately 5 cm. below the EMF probe. The frequency response, mechanical impedance characteristics, and calibration procedure of these calipers have been reported.[11] For calculation of the instantaneous aortic lumen area, the vessel wall was assumed to be 0.5 mm. thick. The pressure was obtained by using a 15-cm. long polyethylene catheter (PE No. 205) which had lateral pressure taps. The catheter was introduced via the left subclavian artery so that the pressure tap was under the calipers. The catheter was connected to a Statham P23Db strain gauge. A Sanborn No. 350 series strain-gauge amplifier was used. The frequency response of the catheter-gauge-amplifier system was evaluated with a sine-wave generator prior to each experiment and was required to be flat ±5 per cent to 25 cycles per second. Both flow and pressure were varied by infusing the dog with isoproterenol and methoxamine, and by producing anoxia and acute hemorrhage. The electrical signals which represented the pressure, flow, and vessel diameter were recorded on an Ampex multichannel electromagnetic tape system for later computation. The signal from the electromagnetic tape which represented the pressure pulse was divided and one part was recorded on a direct-writing oscillograph. The other part of the signal was fed into the problem board of a Donner Model 3000 analogue computer. This signal was then differentiated to obtain $\delta p/\delta t$, which was then used as the forcing function to solve Equation 1. The value of "a" was adjusted to give an as-

Table I. Peak flow EMF (x) versus peak flow $\delta p/\delta t$ (y)

Experiment number	Regression equation (cm.³/sec.)	Standard error of estimate (cm.³/sec.)	Average peak flow (cm.³/sec.)	Correlation coefficient
1.	$y = +9.62 + 0.84x$	±2.30	106.4	.98
2.	$y = -17.56 + 1.64x$	6.18	78.2	.91
3.	$y = +4.02 + 0.99x$	3.03	100.1	.98
4.	$y = -1.95 + 1.05x$	1.62	68.5	.92
5.	$y = -0.23 + 0.89x$	3.44	94.3	.97
6.	$y = +7.68 + 0.89x$	8.89	108.4	.98
7.	$y = +4.92 + 1.16x$	7.39	116.4	.95
8.	$y = -1.11 + 0.92x$	6.10	65.4	.98
9.	$y = +1.20 + 1.07x$	7.94	88.8	.94
10.	$y = -13.67 + 1.06x$	6.38	125.4	.97

sumed zero velocity, w, at the end of diastole during the control state, and was then left untouched. A Sanborn eight-channel direct-writing oscillograph was used for all written recordings.

In each experiment, 25 separate sets of simultaneous curves were analyzed. For reasons previously noted in the introduction, only the peak-to-nadir values were measured. The peak-to-nadir amplitude of the first curve in the control series was set equal to the value of peak-to-nadir flow obtained by the EMF. Since the pressure time derivative method theoretically measures velocity, the flow values were obtained by multiplying the velocity by the greatest cross-sectional area of the vessel. Standard statistical methods were employed in the evaluation of the data. The correlation coefficient, line of regression, and a standard error of estimate for the line were calculated for each experiment.

Results

In the 10 experiments the pulse pressure ranged from 25 to 120 cm. H_2O, and the peak flow from 20 to 155 cm.^{3}/sec. In Fig. 1, the flow curves obtained by the EMF and the pressure time derivative method over a wide range of flow and pressure are shown. The general configuration of these curves is similar, but definite differences in shape can be seen, especially after the administration of isoproterenol (column *B*). Data which compare the EMF peak flow with the $\delta p/\delta t$ peak flow calculated from radius values are shown in Table I. Data were also calculated on the assumption that radius remained constant throughout each experiment. In scatter graphs of these latter calculations the correlation with EMF results was not visibly so good as the correlation seen when the *change in radius* was included in the calculations. However, statistically, no difference could be shown between the "constant radius" and "variable radius" results. Therefore, it would appear that useful estimates of peak blood flow may be obtained without correction for changes in vessel radius. Although the individual regression lines varied significantly at the 0.5 per cent level and cannot be combined, the standard error of estimate was less than ±10 per cent of the average peak-to-nadir flow in all cases. Note that the slope of the regression lines varied from 0.84 to 1.64, and the intercepts from −17.5 to +9.62 cm.^{3}/sec.

Discussion

The frictional properties of blood flow in the aorta are small compared to the inertial properties. Therefore, the friction term (aw) in Equation 1 is small compared to the inertial term $\left(\rho\frac{\delta w}{\delta t}\right)$. To the extent that this is true, the solution of Equation 1, (w), consists primarily of an integration of $\frac{\delta p}{\delta t}$. This would imply that the velocity, w, would be proportional to the aortic pressure, and raises the question whether the pulse pressure itself might not correlate with the EMF peak flow as well as the $\frac{\delta p}{\delta t}$ method. Through the use of identical methods of analyses on the data of the foregoing studies, the pressure time derivative method was *found to be uniformly better in each* experiment than the pulse pressure method for the estimation of peak-to-nadir flows.

The study of Jones and associates was based on comparison of average flow measurements estimated by the dye-dilution method with the areas under the computed flow curves. No effort was made to compare instantaneous values. The present study is *intended to extend these findings for the* case of instantaneous flow.

It would appear from this study as well as from that of Jones and associates that this simple method should find wide application to human cardiovascular physiology if directional changes in stroke volume and peak flows are the only objectives of interest.

Summary

The peak flow estimated by the pressure time derivative method was compared to the peak flow estimated by a Kolin electromagnetic flowmeter (EMF) in the descending *thoracic aorta of 10 dogs. Under the* conditions of this experiment, correlation of peak flow measured by the EMF with that obtained by the pressure time derivative method was good. This method should prove useful in the estimation of changes in peak blood flow. At present, the pressure time derivative method is not self-calibrat-

ing, so that indirect calibrating methods, such as an indicator-dilution technique, must be used to obtain quantitative results.

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Case reports

Cardiac Hodgkin's disease
A clinical, hemodynamic, and angiocardiographic evaluation of a case

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Although involvement of the heart and pericardium by malignant lymphoma is not a rare finding at the time of postmortem examination,[1-6] antemortem diagnosis of this site of involvement is generally quite difficult. A review of the abundant literature concerning Hodgkin's disease fails to reveal any single instance in which cardiac catheterization and angiographic studies have been performed in a patient who was suspected of having cardiac involvement by the tumor. We have recently had the opportunity to study a patient with cardiac Hodgkin's disease in this manner prior to and after the administration of deep x-ray therapy to the mediastinum; the patient showed an excellent clinical and physiologic response to irradiation.

Case report

T. S. (No. 02-10-28) is a 30-year-old man in whom the diagnosis of mediastinal Hodgkin's disease had been established by biopsy at operation 3 years prior to admission, after the discovery on a chest roentgenogram of a mediastinal mass (Fig. 1). At the time of this exploratory thoracotomy a pericardial effusion was present, but no tumor nodules were observed within the pericardium. A pericardiopleural window was created in an attempt to prevent compressive effects on the heart. Postoperatively, he received 3,000 roentgens of irradiation tumor dose to the mediastinum, and during the ensuing 3 months the mass disappeared. Four months after operation a supraclavicular mass became apparent, and this was treated successfully with 3,000 roentgens of irradiation. Three months after this he developed splenomegaly, which spontaneously regressed in the next 4 to 5 months. There was then no evidence of active Hodgkin's disease, and the patient was totally asymptomatic. Chest x-ray examination at this time showed the heart to be at the upper limits of normal size. Four months prior to admission he developed cough, malaise, and episodes of pressing substernal pain and dyspnea after exertion. In the week preceding hospitalization there had been rapid progression of these difficulties. Large pulsations in the neck had become apparent to him. It was of interest also that in the past month his wife and 3 children each had had upper respiratory infections, presumably viral in etiology.

On examination he appeared to be moderately dyspneic at rest but not chronically ill. The blood pressure was 100/70 mm. Hg, pulse 110, and temperature 38.6° C. No lymphadenopathy was noted, and the spleen could not be palpated. There were vigorous "a" waves observed in the jugular veins, which were moderately distended at 45 degrees elevation. The heart was palpably enlarged, with

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a left ventricular lift; a long Grade 3/6 murmur was audible along the left sternal border, becoming ejection type in quality toward the pulmonic area. Only a single component of the second sound was heard at the base (Fig. 2), and the presence of an ejection sound at the apex was questioned. The liver descended 4 cm. below the subcostal margin and was pulsating. No peripheral edema was present.

Venous pressure was 190 mm. of saline, and circulation time was 22 seconds. The electrocardiogram demonstrated normal sinus rhythm with first-degree atrioventricular block and low voltage suggestive of pericardial effusion (Fig. 3). Roentgenographic examination showed generalized cardiac enlargement but adequate pulsation was seen fluoroscopically (Fig. 1). Hemogram and liver and kidney function tests were all normal.

He was placed on bed rest, digitalized, given diuretics, and, although he lost 3.5 kilograms of weight during the next 5 days, he felt little improved. The electrocardiogram now showed intermittent 2:1 atrioventricular block. The assumption was made that there was involvement of the heart by the tumor, and because of the rapid progression of symptoms a dose of 150 roentgens of irradiation was given immediately. It was believed that cardiac catheterization could picture more precisely the nature of the heart disease.

The right ventricle was easily entered, but some difficulty was encountered in passing the catheter into the pulmonary artery, and it was evident that a significant pressure gradient existed between the right ventricle, the infundibulum, and the main pulmonary artery (Fig. 4). Because 2:1 atrioventricular block was present during the catheterization, and the atrium was frequently contracting at the time the tricuspid valve was closed, right atrial "a" waves varied from 6 to 20 mm. Hg. A selective angiocardiogram with injection of radiopaque dye into the right ventricle revealed the presence of a large mass which compressed the pulmonary artery and right ventricular outflow tract, as well as a polypoid mass which extended into the cavity of the right ventricle (Fig. 5). Late films in the series showed an increased distance between the cavity of the left ventricle and the left border of the cardiac silhouette, suggesting either a thickened myocardium or effusion. However, no fluid was obtained by pericardiocentesis.

During the next 10 days a dose of 1,480 roentgens of irradiation was administered to the mediastinum, with great clinical improvement during the latter part of this period. Within 1 week after the irradiation, 2:1 atrioventricular block had disappeared and prolongation of the P-R interval became less, prominence of the venous "a" waves diminished, and the murmur was apparent only after exercise.

One month after therapy the patient was entirely asymptomatic, with normal exercise tolerance. Heart block was no longer present (Fig. 3), and over-all cardiac size had diminished (Fig. 1). At repeat catheterization the peak right ventricular systolic pressure was no longer elevated, although end-diastolic pressure was slightly above normal (Fig. 4).

Discussion

Although a tissue diagnosis of myocardial infiltration by Hodgkin's disease has not been obtained in this patient, in view of the previous mediastinal lesion and the present clinical course, particularly in regard to the response to irradiation, there seems to be little doubt as to the etiology of the cardiac disease. The specific area of the heart which is involved by the tumor in this patient is quite unique, for although ventricular lesions have been described, atrial and tricuspid localization of the disease has been recorded in several reports[7-9] as the usual occurrence. Hodgkin's disease which produces obstruction to right ventricular outflow has not been discussed previously.

The incidence of secondary involvement of the heart and pericardium by Hodgkin's disease varies from 2 to 25 per cent in



Fig. 1. *Left:* Chest x-ray film taken at the time of discovery of Hodgkin's disease, showing the mediastinal mass and a normal cardiac contour. *Center:* At the time of hospitalization there was gross cardiomegaly. *Right:* Diminution in the size of the heart after irradiation. An irregular outline at the apical border can be seen.

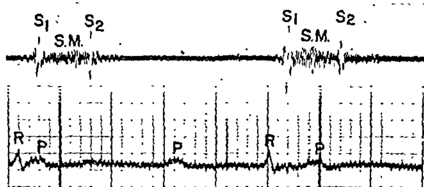


Fig. 2. Phonocardiogram recorded at the left sternal border over the third intercostal space; 2:1 atrioventricular block is present. A long systolic murmur (*S.M.*) and single second sound (S_2) are present, and the first heart sound (S_1) is not unusual.

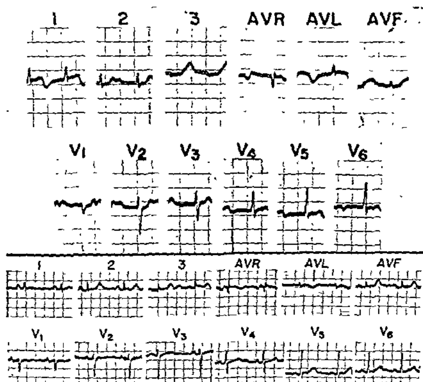


Fig. 3. *Top:* Admission electrocardiogram on May 1, 1961. *Bottom:* Electrocardiogram on June 19, 1961, one month after therapy.

autopsy studies.[1,2] It would appear that pericardial involvement is much more frequent than myocardial. Tumor may be present diffusely or as discrete nodules,[10] yet even in the presence of extensive involvement the suggestive physical signs may be minimal.[2] Scott and Garvin[11] have stated that the most important sign of cardiac invasion in a patient with malignant disease is the appearance of congestive heart failure without other apparent cause. The development of cardiac arrhythmias under similar conditions is also highly suggestive.[12]

Because Hodgkin's disease is thought of as a tumor condition of multicentric origin, the cardiac lesions probably begin locally. Endocardial involvement is exceedingly unusual; this may be attributed to the avascularity of this tissue.[6,11] The polypoid

Congenital pericardial arteriovenous fistula

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A continuous, machinery-like murmur over the precordium is usually due to a patent ductus arteriosus. When the murmur is localized to the pulmonic area, this diagnosis seems to be justified without further diagnostic explorations, and the patient is accepted for operation. As a rule, the surgeon will then confirm the diagnosis. However, in rare cases he will find a closed ductus and has to seek another explanation for the murmur.

On the other hand, when the location of the murmur is atypical, a correct preoperative diagnosis can usually be made with the help of angiocardiography. Such a case will now be described.

Case report

J. S. (370320/61), a 21-year-old man, was first seen in 1958. He had never had any symptoms, and in school he had passed repeated routine medical examinations as healthy. He could not remember any trauma to the chest. A murmur was first heard in 1956, when he was in military service.

At examination there was no cyanosis, no clubbing, no cutaneous vascular malformations, and his general condition was good. A continuous murmur without a thrill was heard just inside the left mammilla. The murmur had its maximum intensity around the second heart sound (Fig. 1) and became louder in inspiration. A 12-lead electrocardiogram and roentgenologic examination of the chest were normal. An atypical ductus arteriosus or a pulmonary arteriovenous fistula was suspected. However, when the right side of the heart was catheterized, the oxygen saturation and the pressures, as well as an angiocardiogram from the right ventricle, were quite normal.

The probable diagnosis became an arteriovenous fistula of the chest wall or the coronary circulation, but further exploration was postponed and the patient was discharged.

When seen again in May, 1961, he was still symptom-free, and the physical signs were essentially unchanged since 1958, but the murmur was now heard over a larger area. The electrocardiogram, chest fluorograms, and working capacity were still normal. The blood volume, determined with Evans blue dye, was 5,070 ml.

A thoracic aortogram from the aorta ascendens revealed a nest of tortuous vessels in the anterior left thorax, with arterial supply from the left internal mammary artery and the left inferior phrenic artery. The coronary arteries were normal. Later, the aorta was recatheterized, and arteriography was performed with the tip of an end-hole catheter in the left internal mammary artery (Fig. 2). One clearly sees the arterial supply from the superior phrenic artery and the mammary artery, the location of the fistula between the heart and the chest wall, probably on the pericardium, and the venous drainage to the left pulmonary vein. Finally, a second injection with the tip of a side-hole catheter in the aorta above the diaphragm showed the enlarged left inferior phrenic artery (Fig. 3) also supplying the aneurysm.

In June, 1961, he was operated on. The fistula was situated on the anterior mediastinal surface of the pericardium, with afferent arteries from the internal mammary artery, the thoracic aorta, and, through the diaphragm, the inferior phrenic artery. The main venous drainage was to the lingula lobe, which here was adherent to the pericardium (Fig. 4). There was a palpable thrill over the fistula. Com-

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mass seen in the right ventricle of this patient may, however, be of endocardial origin.

Summary

A unique case of cardiac involvement by Hodgkin's disease has been demonstrated by cardiac catheterization and angiocardiography. An excellent response was obtained with radiotherapy.

Addendum

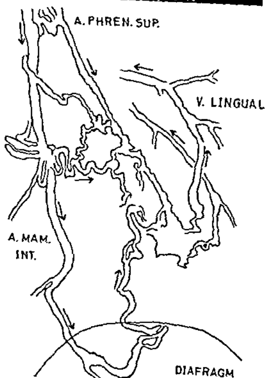
Seven months after the last hospitalization the patient again returned with increasing dyspnea and 3:1 atrioventricular block, which had developed within 1 week. Because of the rapid progression of symptoms, the patient was placed on oral prednisone, in addition to receiving about 1,200 roentgens of irradiation to the heart. Rapid improvement and disappearance of the atrioventricular block followed. One and one-half months after this latest episode the patient is again without symptoms.

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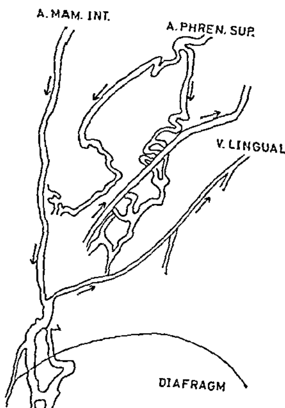


Fig. 2. Arteriograms from the left internal mammary artery. *Left:* Anteroposterior projection. *R:* .. projection. Arrows in the diagrams indicate the direction of blood flow.

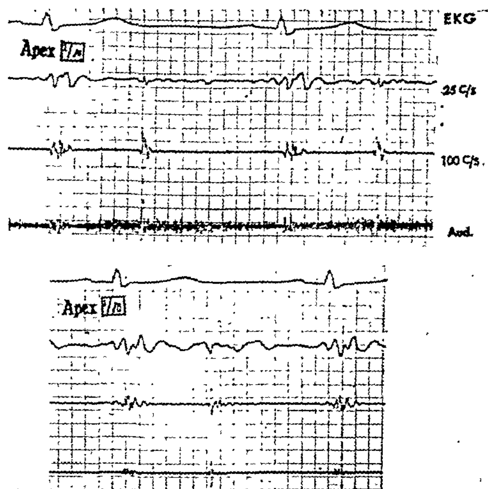


Fig 1. Apical phonocardiograms before and after the operation. Paper speed of 100 mm. per second. Top: Preoperative. *Bottom:* Postoperative.

pression of the largest arteries did not release the Nicoladoni-Branham sign in the direct brachial arterial pressure curve. All afferent and efferent vessels were ligated and divided. The postoperative course was uneventful and no murmur could be heard (Fig 1).

Discussion

Embryologically, arteries and veins differentiate from an anastomosing network of primitive vessels. In normal man, arteriovenous anastomoses are present in many organs, where they may rapidly influence the perfusion and distribution of blood. They were first described by G. F. Meckel (1815-1820) in the pulmonary, and by J. Müller (1835) in the systemic circulation. Anastomoses are present subepicardially,[1] but, to our knowledge, they have not been reported to occur in the pericardium.

The congenital arteriovenous fistulas proper may be apparent at birth, but not seldom become manifest in the second decade or later.[2] Their growth is possibly influenced by external factors, such as trauma, muscle exertion,[3] and metabolic[4] and chemical[5] influences. Thus, some "acquired" fistulas may be due not to new-formed but to activation of preformed anastomoses.

The congenital fistulas are rare. They are usually localized to the extremities, the neck, or the head, but rarely to the chest. The largest group here is the pulmonary arteriovenous fistulas, often combined with hereditary telangiectasis. Winslow[6] early observed a communication between an esophageal artery and a lung vein. The artery originated, together with a left bronchial artery, from the first

Table I. Some conditions which cause a continuous precordial murmur

I. Intrathoracic
   A. Cardiac
      1. Ruptured aneurysm of sinus of Valsalva
      2. Ventricular septal defect with aortic or pulmonary regurgitation
      3. Coronary artery fistula
      4. Aortic stenosis and regurgitation
   B. Extracardiac
      1. Patent ductus arteriosus
      2. Aorticopulmonary septal defect
      3. Pulmonary atresia with bronchial-pulmonary anastomoses
      4. Peripheral pulmonary stenosis, single or multiple
      5. Coarctation of aorta with collaterals
      6. Ruptured aortic aneurysm
      7. Arteriovenous shunts
         Pulmonary
         Systemic
         Systemic-pulmonary
      8. Lactating mamma
      9. Sternal marrow metastases

II. Extrathoracic (transmitted)
   Venous hum from the neck or, rarely, the abdomen
   Arteriovenous shunts

Normally, the medial branch of the inferior phrenic artery anastomoses with the internal mammary artery and its branches, the pericardiophrenic and musculophrenic arteries. These latter arteries give branches to the wide-meshed subpleural plexus of Turner, together with pericardial and bronchial arteries from the aorta. Thus, there are normally many anastomoses between the arteries involved in the fistula of this case.

Continuous precordial murmurs often first lead to the diagnosis of a patent ductus arteriosus. Table I lists some of the congenital and acquired conditions which may cause a similar murmur. In our case the murmur became louder with inspiration. This is also true of pericardial friction rubs, probably because of a stretching effect on the pericardium.[22] The tortuosity of the vessels might be influenced by the same factor, or by widening of the pulmonary veins. The volume of blood which is shunted to the left atrium would rather be expected to decrease in inspiration.

The hemodynamics of arteriovenous shunts depend upon the situation, size, and duration of the fistula.[23,24] Although uncommon as the cause of heart failure, these shunts are important because all signs of decompensation may be relieved by closure of the fistula. In our case there were no signs or symptoms of heart failure on clinical examination and right heart catheterization. The blood volume of the patient was not enlarged, which otherwise may long anticipate heart failure. Thus, the shunted volume of blood was probably small. This is supported, too, by the nonappearance of bradycardia (Nicoladoni-Branham's sign) when the arteries were clamped, which thereby increased the peripheral resistance and pressure.

Because spontaneous closure of a fistula is extremely rare, the recommended therapy is early operation. The reason for this is the strong tendency of the fistulas to enlarge with time and cause local symptoms due to pressure, infection, or rupture, and systemic symptoms due to high-output heart failure.

Summary

A young man with a continuous murmur was shown by means of aortography and arteriography of the internal mammary artery to have an arteriovenous fistula on the pericardium which caused a systemic-pulmonary shunt. The fistula was operated on and closed.

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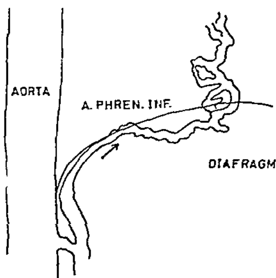


Fig. 3. Aortogram, visualizing the left inferior phrenic artery.

intercostal artery. Maier and associates[7] reported one case of a hemangiomatous fistula under the left breast, and another case of a pulmonary fistula on one side and a fistula of the chest wall on the other, causing hemoptysis and notching of the ribs, respectively. Five cases of fistulas in the posterior chest wall[1,8-10] have been described, and two cases of fistulas between the subclavian artery and vein.[11,12] We have found only one case of communication between the internal mammary vessels,[13] and one case of communication between the left internal mammary artery and the ductus venosus.[14] In their textbook, Levine and Harvey[15] mention three cases of arteriovenous fistula of the chest wall; these, however, seem to lack anatomic verification. Among the cases of Fisher and Johnson[8] is that of a 5-year-old girl with multiple subcutaneous arteriovenous fistulas of the face, neck, scalp, chest, left labia, and buttocks, and submucous hemangiomas in the oral cavity, pharynx, and larynx.

Subepicardial hemangiomas as an unexpected finding at autopsy have been reported[16-19]—with rupture which caused fatal hemopericardium in one case.[20]

The arteriovenous shunt in our case provided communication of systemic arteries with pulmonary veins. In both ontogenesis and phylogenesis there are many examples of intimate connection between the systemic and pulmonary circulations.[21] The early observation of Winslow was mentioned above, and one of the cases of arteriovenous fistula of the posterior chest wall was another example of systemic-pulmonary communications.[10] On the other hand, many pulmonary arteriovenous aneurysms receive systemic arterial supply.

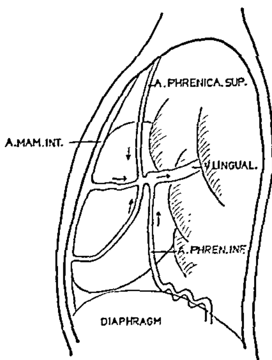


Fig. 4. The surgeon's impression of the fistula.

Antibiotic therapy of bacterial endocarditis

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The clinical features of bacterial endocarditis have been well presented elsewhere,[1-8] and this discussion is restricted to its therapeutic management. For clarity and conciseness these questions are considered in turn: When should antibiotic therapy be started? Which drugs should be employed? In what dosage? What methods of administration should be used? How long should therapy be continued? What results may be anticipated? Commonly encountered management problems are discussed.

Obviously, the sooner adequate antibacterial therapy is established in patients with this infection the less likely is serious or irreparable damage to occur to the heart or other structures. Does this imply that it is wise to commence treatment immediately when the clinical features of the patient's illness point to bacterial endocarditis, or is it more prudent to await the results of blood cultures, which enable one to establish the diagnosis with certainty, and to define the organism and its antibiotic sensitivities?[9]

To a significant degree, the answer to this question depends upon the nature of the infecting organism. Some organisms, such as the staphylococcus, the enterococcus (*Streptococcus fecalis*), and the pneumococcus, are commonly very highly invasive and rapidly destructive, quickly producing marked structural alterations in the heart and elsewhere. By contrast, other organisms, such as the *Streptococcus viridans*, do not behave at all like this. The heart may be infected by them for a prolonged period without significant architectural changes resulting. Clearly, in dealing with organisms of the first type it is mandatory to start specific treatment at the earliest moment. Irreversible damage may be the product of even a brief delay. On the other hand, a short postponement while the results of blood cultures are awaited may be highly advantageous in dealing with infections of the latter type.

The clinical diagnosis of bacterial endocarditis can be enormously difficult.[10-12] The so-called "classic features" of the illness, clubbing, changing murmurs, petechiae, splenomegaly, anemia, and hematuria, are very often not present, particularly in the early course. Nonspecific manifestations of infection are generally the most prominent features. Cardiac alterations may be unimpressive. Embolic occurrences frequently mislead by distracting attention from the heart to some seemingly unrelated peripheral occurrence, often dramatic in its presentation. The diagnosis of bacterial endocarditis can be made consistently only if its presence is suspected whenever a patient with any degree of cardiac abnormality begins to show manifestations of an infection. To precipitously initiate antibacterial therapy in all such

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has shown to be most effective against the particular organism believed to be infecting the patient. Here, again, analysis of the total setting of the infection should assist in the recognition of the organism most likely to be responsible, and the design of the most effective program of treatment.

It follows that the optimal management of a patient with bacterial endocarditis requires that the sensitivity of the infecting organism to all pertinent antibiotics be determined. Jawetz[21] has recently suggested that the determination of the antibacterial potency of various combinations of antibiotics may be advantageous when one is dealing with resistant organisms, such as the staphylococcus. If practicable, one should employ the tube dilution method followed by subculture to determine bactericidal end points. This gives much more valuable information than the disks. In selecting an antibiotic, one must not be misled by disk tests which show relatively large clear zones around the bacteriostatic agents, such as the tetracyclines, which should not be given preference over bactericidal agents, regardless.

The serum inhibition test may be of some help in evaluating the adequacy of an antibacterial program which is in progress.[19] In this test the bacteriostatic activity of serial dilutions of the patient's serum is determined during the course of therapy. If a 1 to 16 dilution of serum inhibits growth of the infecting organism, sufficient antimicrobial activity is presumed to be present. This assumption is not always correct, however.

Although these in vitro tests are helpful in designing an effective antibacterial program, they should not be followed slavishly, since they do not always accurately reflect in vivo results. An antibiotic may appear to be highly effective against the infecting organism in vitro and yet fail miserably in the patient, and vice versa. It is the total clinical response of the patient as determined by day-to-day observation which tells the story, and laboratory results which are not in agreement with such clinical information should be regarded with skepticism.

Should a single or several antibiotics be employed? In general, two or more antibiotics should never be used if one alone is effective, since to do so increases the opportunity for drug reactions and adds to the confusion when they do occur. On the other hand, a combination of penicillin and streptomycin should always be given when dealing with the enterococcus (*Streptococcus fecalis*). Likewise, a combination of two or more bactericidal agents sometimes appears to bring the best results in staphylococcal infections,[19-22] and in those due to gram-negative bacilli.

Penicillin is so eminently the drug of choice in all but a few instances of bacterial endocarditis because of its clot-penetrating and bactericidal and nontoxic qualities that it should be given even in the presence of penicillin hypersensitivity, unless some other bactericidal agent is demonstrated to have equal therapeutic merit. Thus, vancomycin might be substituted for penicillin against a staphylococcal infection if sensitivity studies indicated its efficacy. In instances of penicillin sensitivity, chloroprocaine penicillin O may be tried or an antihistamine given, or prednisone (Meticorten) administered concomitantly with the penicillin. If the penicillin must be started without delay, the steroid should be given intravenously initially, and not by mouth.

The dosage plan adopted must be one which will insure the attainment of a bactericidal level throughout the entire fibrin-platelet matrix. Experience has indicated that a serum concentration 5 to 10 times the in vitro sensitivity of the infecting organism will achieve this. Theoretically, at least in the case of penicillin, peaks of antibiotic concentration in the blood are preferable to the maintenance of sustained levels, suggesting that intermittency of administration may be more effective than constancy.[23-27] For this reason we prefer aqueous crystalline penicillin G, given intramuscularly every 6 hours.

The daily dosage of penicillin required for a particular organism may be estimated by applying the crude rule of thumb that for each million units of penicillin given intramuscularly in divided dosages per day a blood level of approximately 1 unit is achieved. Since the therapeutic goal is to secure a blood level 5 to 10 times the sensitivity of the organism, it is simple arithmetic to devise an appropriate dosage

instances without obtaining confirmation of one's clinical suspicion by positive blood cultures would, of course, condemn a large number of patients to a program which would be unnecessary, painful, expensive, and fraught with the special hazards of antibiotic agents

It becomes important, therefore, to be able to estimate with reasonable clinical accuracy whether a patient suspected of having bacterial endocarditis is infected by an invasive, destructive organism or by one which is relatively less so. How can one make such a judgment?

The setting in which the illness occurs can be very informative. Thus, the occurrence of a recent staphylococcal infection of the skin or elsewhere, an abortion, manipulation of the urinary tract, a heart operation, an episode of pneumonia or of meningitis are all circumstances in which the destructive form of endocarditis would be anticipated. Among likely candidates for this type of endocardial infection are elderly individuals, diabetic patients, persons who have neoplasms or leukemia as well as other disorders, such as systemic lupus, in which there may be abnormal immunity, and patients receiving prophylactic antibiotics. Acute onset and brisk progress of symptoms, with chills and toxicity, profuse embolic occurrences, changing murmurs or a murmur heard in a heart previously regarded as normal, the early or fast development of anemia or marked hematuria, a significant leukocytosis (or a depressed white blood cell count), and the rapid onset of cardiac or renal impairment are all clinical points which suggest a destructive bacterial agent. Signs of suppurative emboli are, of course, pathognomonic.

If a summation of these features indicates the likelihood of a relatively destructive organism, treatment should be started after a few hours during which a series of blood cultures are obtained for future guidance. If they indicate a relatively benign infection, and the general condition of the patient warrants, a delay of a few days until an organism has been isolated and its antibiotic sensitivites are determined will greatly assist sound therapeutic planning. If in doubt, one should not delay.

Blood cultures should be obtained in a planned way, not catch-as-catch-can. It is well to take six or eight cultures, spaced at equal intervals, over a period of 36 or 48 hours. It has been shown that, generally, if bacteremia is present, one or more of these six to eight cultures will be positive; conversely, it is unlikely that the etiological organism will be recovered on subsequent cultures if those in this initial batch are all negative. An important exception to this rule is the patient who has been taking antibiotics prior to the performance of the cultures. Even a short course of antibiotics may clear the blood stream of organisms for a number of days and thus compound the difficulties of establishing a definite diagnosis. One can only wait and reculture. Penicillinase should be added to the culture medium if penicillin has been given. Both aerobic (tryptokase-soy or tryptose phosphate) and anaerobic (thioglycollate) media should be used, and several cultures should be incubated at reduced carbon-dioxide tension. Cultures should not be discarded as negative until observed for fully 2 weeks, in order not to overlook slow-growing organisms, such as Bacteroides.

In considering the antibiotic to be employed, and the dosage, one must understand the nature of the pathologic process.[13-17] The bacteria become imbedded within a matrix of fibrin and platelets covering the affected endocardium. When the bacteria are invasive and destructive, abscesses may extend into the heart muscle and the valve rings and become disseminated elsewhere as well. Since these lesions are relatively avascular, little reliance can be placed upon normal cellular and humoral defense mechanisms to get rid of the bacteria. To be effective in such circumstances the antibiotic must be able to penetrate deeply into these areas, and have the ability to kill the bacteria as they are reached. Bactericidal potency is essential; bacteriostasis does not suffice. Therefore, the drug of choice in each instance is that bactericidal agent which has the greatest killing power, as demonstrated by in vitro techniques. While waiting to receive this information from the laboratory, one should employ the bactericidal agent or combination of agents which experience

isolated occurrences need not be regarded necessarily as indications of inadequate therapy.

It is important to give the patient an opportunity to "settle down" to a given program of treatment. Frequent, precipitous alterations of therapy create such instability that it becomes impossible to judge from the clinical course what is going on, and to recognize the most reasonable solution to whatever problems exist.

There are a number of therapeutic considerations which deserve individual attention. Most instances of subacute endocarditis are caused by streptococci of the viridans group, which are sensitive to 0.2 unit of penicillin per cubic centimeter of serum or less. These respond well to 1,000,000 units of aqueous crystalline potassium penicillin G given intramuscularly every 6 hours for not less than 4 weeks. In the unusual instances in which the *Streptococcus viridans* is relatively resistant, an increased dosage of penicillin is administered, the "rule of thumb" mentioned above being applied, and streptomycin and Benemid are given additionally.

Approximately 10 to 15 per cent of the patients with bacterial endocarditis have persistently negative blood cultures. The mortality rate in this group is excessively high, and most observers agree that they should be treated with a combination of 20,000,000 units of penicillin and streptomycin for not less than 4 weeks. Benemid should also be used. Two grams of streptomycin should be given daily for the first 2 weeks, and then 1 Gm.

This same schedule should be followed in those instances of subacute endocarditis in which it is deemed wise to commence treatment before there is time for identification of the responsible organism and determination of its antibiotic sensitivities. Later, when this information is at hand, the schedule can be altered to meet the particular requirements of the organism isolated.

The mortality from endocarditis due to the enterococcus (*Streptococcus fecalis*) is still inordinately high. This is due in part to the fact that the organism is destructive and invasive, and also to the fact that it is oftentimes resistant to penicillin, or rapidly becomes so. Sometimes, massive quantities of antibiotic are required to overcome it. If this infection is suspected from the clinical setting (elderly individuals, the presence of various chronic illnesses, infection of the urinary tract, urological manipulation, postpartum state, or abortion), treatment should be started with not less that 20,000,000 units of penicillin daily, with streptomycin and Benemid. The ultimate dosage of penicillin will depend upon the in vitro sensitivity tests. It is basic that enterococcal infections be recognized and brought under control at the earliest moment, and that sufficient penicillin be given from the outset, since this organism may rapidly reach a degree of resistance which is difficult or impossible to overcome.

In this clinic and elsewhere the concomitance of pneumococcal meningitis and endocarditis has been noted.[31] Commonly, the clinical manifestations of meningitis have been predominant initially, and the endocardial lesion has been noted only subsequently when the patient developed cardiac failure due to injury to the aortic valve. This possibility should be considered in the therapeutic management of patients with pneumococcal meningitis. The heart should be checked daily for evidences of incipient endocarditis, with frequent review for several months during the convalescent period.

Staphylococcal endocarditis continues to be associated with a very high mortality rate, due in part to the invasive and destructive potentialities of the organisms, and also to the fact that 50 per cent of these organisms are resistant to penicillin. The advent of new agents, such as methicillin, which are not significantly affected by penicillinase may improve the outlook for such patients, although it must be recalled that it is not through penicillinase production alone that the staphylococcus becomes resistant to penicillin, since resistant mutants may also appear. There is some evidence that *Staphylococcus albus* strains may become resistant to methicillin during therapy with some frequency, but this does not appear to be the case with *Staphylococcus aureus*. While awaiting the results of in vitro sensitivity tests, one may start treatment either with the intravenous administration of 40,000,000 to 60,000,000

schedule, once the sensitivity of the organism is known. Thus, if the organism has a penicillin sensitivity of 2 units, one should give 10,000,000 to 20,000,000 units of the antibiotic per day. In the patient with renal disease it may be important to note that penicillin G is a potassium salt—approximately 1.5 mEq. of potassium is contained in a million units. Staphcillin and penicillin O are sodium salts.

In regard to methods of administration, the basic requirement is that an adequate concentration of antibiotic be achieved in the patient's blood to meet the objectives outlined above; *how* this is accomplished resolves itself into such practical issues as the comfort of the patient, the costs of the drug, and covenience. It is generally not practicable to give more than 4,000,000 to 6,000,000 units of penicillin intramuscularly daily for a protracted period. If larger dosages are needed, aliquots of the daily dosage required should be given in 5 per cent glucose by continuous, intravenous drip. Small amounts of heparin may prevent venous thromboses. Venous cut-downs and femoral vein catheters should be avoided. Meticulous care should be given to prevent bacterial contamination of the venipuncture site and the intravenous set, since secondary staphylococcal or *Pseudomonas aeruginosa* infections may result from carelessness. Penicillin levels may be enhanced by the use of probenecid (Benemid), 0.5 Gm. every 6 hours. This is advantageous whenever high serum levels of penicillin are to be achieved, as in enterococcal or staphylococcal infections.

Although there are no theoretical objections to the use of oral penicillin, the practical fact is that some patients may fail to absorb the drug from the intestinal tract in adequate concentration; and since it is not usually feasible to determine the levels of penicillin in the blood during the course of treatment, avoidable risks may be involved in the employment of the oral route. Oral penicillin is emphatically to be avoided if the organism is at all resistant to penicillin.[29] Oral penicillin is sometimes given to supplement parenteral dosage, or to prolong an abbreviated course of parenteral penicillin. When this is done, it is probably wise to obtain serial spot checks of the antimicrobial activity of serum dilutions.

The optimal duration of antibiotic treatment has been a matter of controversy.[29,30] When dealing with invasive and destructive and relatively penicillin-resistant infections, such as those produced by the staphylococcus, the enterococcus (*Streptococcus fecalis*), and the pneumococcus, all agree that treatment should be continued for 4 to 6 weeks. On the other hand, when dealing with organisms which are highly sensitive to penicillin, some observers have advised that the use of a combination of high dosages of penicillin with streptomycin has enabled the total duration of treatment to be reduced to 2 weeks.[19,20] Presumably, the streptomycin enhances the bactericidal capabilities of the penicillin. We have been loath to discontinue treatment under any circumstances in less than 4 weeks, believing that sufficient time must be given to allow the healing process to become complete. In an infection which has almost 100 per cent mortality it is wise to insure adequate treatment in all instances, even if this occasionally may entail overtreatment.

The adequacy of a given dosage schedule is determined by the day-to-day clinical observation of the patient's total response. If at any time this appears to be unsatisfactory, the dosage should be doubled, or the program otherwise reinforced. In the evaluation of the patient's therapeutic response it is essential, of course, to consider those factors, narrated subsequently, which may cause fever and otherwise mimic continuation of the endocarditis. Sterilization of blood cultures is not enough. This can be achieved despite persistent endocardial infection. When a therapeutic program is adequate, defervescence customarily occurs in 2 to 5 days, with concomitant fall in pulse rate. Concurrently, the patient rapidly develops a sense of well being; sweats and anorexia steadily vanish. A gain in weight and elevation of hemoglobin and red blood cell count are progressive, but several weeks may be required before normal values are reached. The beginning of a reticulocytosis in an anemic patient may be another clue to effective treatment. The sedimentation rate gradually reaches normal. Embolic phenomena and petechiae may continue to appear for many weeks, even though treatment is effective, and

to operate upon the heart has created new problems in endocardial infection, and also brought new solutions. The incidence of postcardiotomy endocardial infections is said to be well under 1 per cent[24,35]; unfortunately, they are frequently produced by organisms with high resistance to antibiotics, such as the staphylococcus. This should be appreciated when a program of treatment has to be designed prior to isolation of the responsible organism, and the determination of its antibiotic sensitivity. One should plan as though the organism is a resistant, destructive one, until laboratory studies prove that it is not. It may be excessively difficult to feel very certain on clinical grounds alone of the existence of endocarditis postoperatively, because fever is frequently the only indicant of its presence, the usual clinical features of endocarditis being absent. Usually, one can only be suspicious, and secure blood cultures. How long to delay starting treatment without positive blood cultures depends upon the height of one's index of suspicion, and the patient's general status. If the index is very high, the wait should be brief since the responsible organisms are often invasive and destructive, as emphasized.

The new therapeutic solutions offered by surgical techniques fall into three groups: first, the correction of abnormal blood flow which predisposes the patient to the development and continuance of endocarditis or endoarteritis; second, the removal from the heart or vessels of foreign material (stitches, patches) which may be the nidus of a postoperative infection, and sustain it despite adequate antibiotics; and third, remodeling or replacement of valves injured during the course of endocarditis. The latter may be of particular benefit to those patients who develop aortic insufficiency as a result of ulcerative endocarditis. Even though cured of infection, a large proportion of these individuals ultimately develop progressive cardiac failure because of the dynamic effects of the lesion. As a rule, such repairs should not be made until the patient is entirely convalescent from the local and general effects of the endocardial infection. On the other hand, if a foreign body is continuing an infection, operation should not be delayed, since eradication of the infection will depend upon removal of the foreign substance. Of course, it may be difficult to be sure on this score. In dealing with infected shunts, it is important in planning treatment to recall that one or more of the heart valves may be secondarily implicated. Thus, an infected ductus may become associated with endocarditis of the aortic, mitral, or other valves. For reasons not clear, an arteriovenous shunt may predispose not only to the development of endoarteritis, but to endocarditis as well.[36] It is generally unwise to attempt correction of such a shunt until the infection has been eradicated and the patient is fully recovered from its effects. However, if one is confronted by a resistant organism which will not respond to very intensive antibiotic therapy, removal of the shunt will take precedence.

It is highly disconcerting when a patient who seemingly has been adequately treated begins abruptly to have fever again. There is an impelling temptation in these circumstances to increase immediately the dosage or change the antibiotics. Such an approach only creates confusion. Rather, one should review the most common causes of fever under these circumstances, and act accordingly. The most common causes of fever are these: inadequate antibiotic program, a drug reaction (including *all drugs* the patient is receiving), an inflammatory reaction at the site of injection of the antibiotic, thrombophlebitis, metastatic suppuration in spleen or elsewhere, super infection due to another organism, an intercurrent infection, activation of an associated disease process, such as rheumatic fever or systemic lupus, embolic occurrences to lungs or elsewhere, incorrect initial diagnosis. A wise plan is to eliminate all but the essential drugs while these various diagnostic possibilities are being pursued. If the patient has a persistent sense of well being and is eating well, if there are no obvious manifestations of an active endocarditis, such as petechiae, etc., and if the antibiotic program is one which theoretically assures blood levels 5 to 10 times the sensitivity of the organism, it is likely that the fever is due to some factor other than inadequate treatment. If there is reasonable doubt about the antibiotic program, intensify it. If the

units of penicillin daily plus Benemid by mouth, or with 8 to 12 Gm. of methicillin intravenously in divided dosages plus Benemid. Methicillin has the disadvantage of being highly expensive at the present time, and, in some instances, of not being so effective against the staphylococcus; on the other hand, methicillin-resistant strains of staphylococci are extremely rare, whereas penicillin-resistant strains are common. Hence, it may prove wiser to start with methicillin and switch to penicillin later if sensitivity studies indicate its efficacy. Because of its established value, vancomycin should also be considered for initial use in the very sick patient, although methicillin is less toxic and easier to administer.

Because of the high mortality rate in staphylococcal endocarditis, and the tendency of the staphylococcus organisms to sometimes develop a degree of resistance which may be insuperable, some observers are reluctant to rely upon one antibiotic, and employ a combination of bactericidal agents with penicillin or methicillin.[22] There is some thought that such combinations may inhibit the development of resistance to penicillin. When combinations are used, it is important that the organism be sensitive to all agents employed. Full dosages of streptomycin, or Chloromycetin, or erythromycin, or novobiocin might be used, singularly or in a variety of combinations. Once the in vitro sensitivity test results are known, a combination of the most effective bactericidal agents may be given in full dosage. We have continued to employ penicillin (or methicillin) as the backbone of our program, unless an insuperable degree of resistance was demonstrated. Benemid is given, of course, to amplify the levels of penicillin.

If the patient fails to respond to such a program within 72 hours, vancomycin should be added, because results with this agent have been very satisfying.[32] This drug must be given intravenously, and since intermittent peak levels are desirable, it should be administered in doses of 0.5 Gm. dissolved in 200 c.c. of 5 per cent dextrose and water, infused over a period of 15 to 30 minutes every 6 hours. If there is a dearth of veins, kanamycin may be given in place of vancomycin. The dosage is 0.6 Gm., given intramuscularly every 6 hours. It should not be given intravenously. Because of the production of auditory damage, the total amount given should be limited to 20 Gm. Renal function may be somewhat impaired. Use of the agent is limited to 10 to 14 days. Should all of the above-mentioned agents fail to achieve a response, bacitracin may be given—20,000 to 25,000 units every 6 hours, intramuscularly. Renal function must be carefully observed.

Treatment of staphylococcal endocarditis should be continued for fully 6 weeks.

Endocarditis due to gram-negative organisms is noteworthy because of its infrequency despite the frequency of bacteremia due to these organisms. This feature may be partly explainable by the fact that gram-negative bacteremia is likely to be symptomatic and, therefore, investigated and treated early, and by the debilitation and attendant high mortality rate characteristic of patients who develop gram-negative bacteremia.

The antibiotics most likely to exert bactericidal activity toward gram-negative organisms are streptomycin, kanamycin, neomycin, polymyxin B, colistin, and penicillin in high concentrations. Toxicity and resistance limit the usefulness of some of these agents. Streptomycin is active toward only about one third of these organisms, and should always be used in combination with another effective agent when endocarditis is treated. Colistin and polymyxin are active toward most Pseudomonas, Klebsiella, and *Escherichia coli*, but they should always be used in large amounts for the treatment of endocarditis, and colistin is probably less toxic in these circumstances. Colistin and polymyxin are ineffective in Proteus infections. *Proteus mirabilis* strains are peculiar in that they are usually susceptible to high concentrations of penicillin, and many *Escherichia coli* strains fall into the same class. Kanamycin is a useful drug in about half of these infections despite its potential toxicity. The successful therapy of endocarditis due to gram-negative organisms is particularly dependent upon precise sensitivity tests and skillful manipulation of drugs and dosages.[33]

The recently acquired ability of surgeons

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picture is very much confused, it may be wisest to discontinue all specific therapy and start anew.

While the treatment is in progress, the patient's dental status should be reviewed, and any infected teeth should be extracted and good oral hygiene instituted. This is oftentimes neglected.

The future outlook of any patient with bacterial endocarditis will be determined by a variety of factors. If the infecting organism is resistant, invasive, and destructive, the odds are poor. The mortality rate of staphylococcal and enterococcal endocarditis still approximates 50 per cent. If embolic occurrences damage an organ, such as the brain, the chances for a good recovery are clearly lessened; this includes the kidneys, which in addition to an embolic nephritis much less commonly may undergo the alterations of glomerulonephritis. How the heart fares will be dependent upon several factors, including the degree of damage produced by whatever primary disease process is underlying the endocarditis, the amount of distortion of valve function the infection induces, and the integrity of the heart muscle. The latter factor is most significant although often not emphasized enough. The myocardium may be adversely affected in several ways. An acute, diffuse myocarditis may ensue, or there may be microinfarcts which lead to diffuse scarring, produced by repeated small coronary emboli. A large coronary embolus may result in major infarction. Mycotic aneurysms of the coronary vessels may do likewise, precipitating failure or death. Organisms, such as the staphylococcus, may produce deep-seated abscesses in the myocardium, or there may be an associated acute myocarditis due to an accompanying rheumatic fever or systemic lupus. Whatever the cause, if an appreciable degree of cardiac failure was present before the endocarditis began, or appears at anytime during the course of treatment, or within 6 months of its completion, the outlook is not good. Patients who develop cardiac failure during these periods tend to do so progressively as time advances, and their prospects are not encouraging, even though they may be readily cured of their infection.

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paired coronary circulation it is necessary to correct the tachycardia promptly. More drastic treatment is usually indicated in such cases than when a similar tachycardia occurs in individuals with a normal coronary circulation.

Other studies have demonstrated that the cerebral circulation also may be affected by a paroxysm of tachycardia and may be reduced as much as 60 per cent during an episode of ventricular tachycardia.[8,25,27] The patient with cerebral arteriosclerosis may develop cerebral vascular insufficiency due to a cardiac arrhythmia, and, if the disturbance is not corrected promptly, permanent cerebral damage may result. Many cerebral strokes are due to unsuspected transient arrhythmias.[1]

Infarction of the kidney may occur without arterial occlusion after an episode of ventricular tachycardia.[6] Measurements of blood flow with the electromagnetic flowmeter indicate that the renal circulation may be markedly impaired during a tachycardia.[4,9] Therefore, in the patient with a borderline renal circulation or uremia it is necessary to correct supraventricular or ventricular tachycardias as promptly as possible.

Chinsky[7] has reported that the serum enzymes (SGOT and SGPT) may rise to very high levels during an attack of ventricular tachycardia. We also have seen a number of patients who developed a marked elevation in the serum transaminase after each episode of supraventricular and ventricular tachycardia.[1] Impairment of the hepatic circulation during the tachycardia is probably responsible for this elevation in the transaminase. The mesenteric circulation may be markedly reduced in the experimental animal during ventricular or supraventricular tachycardia because of reduced cardiac output, blood pressure, and an intense mesenteric angiospasm.[1,9] This mesenteric angiospasm has been recently demonstrated in the experimental animal during rapid tachycardias and irregular rhythms.[1,9] Ischemia results in functional and even morphologic changes in the gastrointestinal tract.[9,27] Nausea, vomiting, hematemesis, abdominal distention, paralytic ileus, and diarrhea, with or without blood, may result from this ischemia which we have termed "mesenteric vascular insufficiency."[1,9,25]

Therefore, the effect of the arrhythmias on the circulation of all the vital target organs requires special consideration. If impairment of the vascular supply of a vital organ already exists, hypotension and reduction in cardiac output during an arrhythmia may cause ischemia of the organ because of angiospasm and the diminished cardiac output. In the patient with a normal circulation the organs may withstand ischemia for relatively long periods of time, and, therefore, it may not be necessary to consider an arrhythmia as grave an emergency or to treat it as heroically as would be required in a patient with an already precarious circulatory status.

Mortality rate of arrhythmias associated with myocardial infarction

The mortality rate of supraventricular tachycardias complicating myocardial infarction is very high. In 1949, Askey[15] reported a mortality rate of 100 per cent in 5 patients. Herrmann and associates,[16] in a more recent study, noted that 10 of 13 of his patients with myocardial infarctions died when ventricular tachycardia supervened. The mortality rate of ventricular tachycardia in patients without myocardial infarctions was much less. More recent mortality statistics indicate that, when supraventricular or ventricular tachycardia follows a myocardial infarction, the mortality rate is 82 per cent.[1] The mortality rate of tachycardias and conduction defects associated with a coronary occlusion was devastating, but this has been markedly improved by vasopressor therapy.

Vasopressor treatment of cardiac arrhythmias and conduction defects

Sympatheticomimetic drugs, such as Neo-Synephrine, noradrenaline, or methoxamine, will often restore regular rhythm in patients with cardiac arrhythmias.[10-14] It is believed by some that the action of these agents is mediated through the autonomic nervous system.[12] However, this should be considered as a direct vasopressor effect because it is possible to convert ventricular and supraventricular tachy-

Fundamentals of clinical cardiology

Recent advances in the treatment of arrhythmias and conduction defects

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It is paradoxical that pharmaceutical agents which are able to correct cardiac arrhythmias may also induce more severe and sometimes fatal irregularities of the heartbeat.[1] Under certain circumstances, many arrhythmias and conduction defects are relatively harmless and may not require treatment.[1] Fortunately, many disturbances of heart rate, rhythm, and conduction revert spontaneously to normal. Therefore, before instituting a course of therapy, the clinician must have several factors clearly in mind; for example: (1) the prognosis of the particular arrhythmia under consideration; (2) its relationship to underlying cardiovascular disease; (3) the relative urgency for correction of the arrhythmia; (4) the possible dangers of the contemplated treatment and how they may be minimized; (5) the choice of methods of administration of various drugs (oral, intramuscular, intravenous, etc.), and the advantages and hazards of each.

Effect of arrhythmias on vital organs

Much of the basic physiology of the arrhythmias remains to be worked out. Deleterious effects of the arrhythmias, such as insufficiency of the coronary,[5,14] cerebral vascular,[2-4,8,36] hepatic,[1,37] renal vascular,[4,9] and mesenteric vascular systems,[9] have only recently been evaluated. This recent information will be useful to clinicians in determining the need for and the degree of urgency of treatment, particularly in the aged patient with narrowing of the arteries.

Patients with an impaired coronary circulation often complain of anginal pain and demonstrate electrocardiographic and morphologic changes of myocardial ischemia during tachycardias and irregular rhythms.[1,5] Recent experimental studies in the dog have demonstrated that during ventricular tachycardia the average reduction in the coronary flow is 60 per cent, and that in atrial tachycardia and fibrillation it is 35 and 40 per cent, respectively.[5] It has been found that when systemic hypotension results during a tachycardia, the coronary flow is reduced. This may result in infarction of the myocardium or cardiac decompensation. These experimental studies suggest that in patients with an im-

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down of catecholamines, which are ever present in the myocardium. The sympathetic nerve endings in the myocardium normally liberate noradrenaline, which may induce arrhythmias. The enzyme *monoamine oxidase*, which is normally present in the myocardium, metabolizes the noradrenaline and thus reduces this irritability. Brewster[18] demonstrated that thyroid inhibits the monoamine oxidase from breaking down the noradrenaline. It may be theorized that the patients with recurrent tachycardias liberate an excess amount of noradrenaline. Therefore, if the thyroxine content is reduced by antithyroid medication, the monoamine oxidase will be free to metabolize the irritating noradrenaline. One might also ask whether these patients had masked Graves disease. Clinical and laboratory observations over a long period of time indicate that these patients are euthyroid.[17]

One of the objections to the hypothyroid treatment of the recurrent tachycardias is that hypercholesterolemia results. However, recent studies have demonstrated that the administration of thyroid analogues, such as tetraiodothyroformic acid, will reduce the serum cholesterol content of these hypothyroid patients while they eat a regular diet.[19a, 19b]

B. Chronic atrial fibrillation. The ventricular rate of patients with chronic atrial fibrillation can usually be controlled by the administration of digitalis. However, it is sometimes impossible to slow the ventricular rate, and congestive cardiac failure supervenes. Recently, 8 patients with rapid chronic atrial fibrillation were treated with radioactive iodine after all other measures had failed to slow the rate. After a hypometabolic state had been induced, the ventricular rates slowed even without the use of digitalis.[1,17] In 3 of the patients the arrhythmias converted to regular sinus rhythm spontaneously. One patient in whom the conversion was spontaneous had chronic atrial fibrillation and a giant left atrium due to rheumatic valvular disease of 17 years' duration.[17]

Digitalis toxicity

Because of the high mortality rate in some types of digitalis-induced arrhythmias and the new advances in the treatment of digitalis toxicity,[20] it is of the utmost importance that this diagnosis always be entertained by the clinician. The problem of intoxication has been increased by the popular use of purified glycosides of digitalis and increased reliance on oral saluretic drugs.[20] Diuretics cause increased urinary excretion of potassium. Hypopotassemia renders the heart more sensitive to digitalis.[20] Overdosage of the purified glycosides is often first evidenced by arrhythmias.[43]

The most important manifestation of digitalis intoxication is the occurrence of arrhythmias. Any type of arrhythmia and conduction disturbance may be caused by digitalis toxicity. Digitalis may act either as a depressant of the conduction system or as an irritant to the myocardium.

The depressant action of digitalis may result in sinoatrial block, intra-atrial block, or atrial standstill. If the A-V node is depressed, conduction defects, such as first-degree or second-degree block or complete A-V dissociation, may occur. Interference dissociation may be regarded as a specific effect of digitalis. When the conduction system in the lower ventricle is depressed, bundle branch block and intraventricular block result.

The various arrhythmias caused by the irritant action of digitalis are atrial fibrillation, atrial flutter, or atrial tachycardia with block. We believe that the latter disturbance, which is considered to have a high mortality rate, is the same as atrial flutter with block.[1] Other investigators[20] do not agree with this interpretation. In one series of patients who had atrial tachycardia with block caused by digitalis, 23 of 39 (60 per cent) died.[20] Ventricular premature systoles are also common manifestations of digitalis overdosage, particularly when digitalis and diuretics are used concomitantly in the patient who has sustained a myocardial infarction. Because both diuretics and the myocardial infarction reduce the myocardial potassium, the heart becomes more sensitive than normal to digitalis.[1,20] In these patients, bursts of multifocal premature beats are warning signs which may precede ventricular tachycardia and ventricular fibrillation. Electrical alternans is often due to digitalis toxic-

cardias to sinus rhythm in denervated hearts by merely restoring the systemic blood pressure with an artificial aortic coarctation.[14] Regular sinus rhythm was restored with vasopressor drugs in 23 of 28 patients who had developed serious cardiac arrhythmias after myocardial infarction. They had all developed hypotension and had serious narrowing or occlusion of the coronary arteries; their condition appeared to be critical. In this series, the arrhythmia in one patient could not be converted, and another patient died 8 hours after sinus rhythm was restored. The disorders of the heartbeat consisted of bigeminal rhythm due to frequent premature ventricular systoles, marked bradycardia, complete heart block, paroxysmal atrial tachycardia, fibrillation, and ventricular tachycardia.[14] Vasopressor treatment alone was successful in "aborting" the cardiac arrhythmias in most of the patients. However, when the rhythm could not be immediately converted, the vasopressor treatment "supported" the coronary and systemic circulations until other antiarrhythmic medication was effective. In animals, when a tachycardia could not be abolished with vasopressors, we could almost always restore the coronary flow by restoring the systemic blood pressure. In other words, vasopressor drugs effectively "support" the coronary circulation until other, slower acting, antiarrhythmic agents take effect. If the blood pressure can be maintained, it is usually not necessary for the clinician to hurry the antiarrhythmic medication.

The restoration of the systemic blood pressure also increases the collateral coronary circulation. It is the maintenance of this collateral circulation which minimizes an area of myocardial necrosis. In addition to reducing the mortality rate, vasopressor treatment limits the area of ischemia and thus reduces the extent of myocardial damage.

Although vasopressor drugs are often effective in converting the arrhythmias, they sometimes cause fatal ventricular fibrillation.[5] Serious prefibrillatory arrhythmias tend to occur when the systolic blood pressure is raised above 180 mm. Hg.[4] Therefore, it is of the utmost importance when the vasopressor drugs are used that the blood pressure be maintained below this arrhythmic-producing level or death may result. In selecting a vasopressor drug to restore regular sinus rhythm, the clinician should use an intravenously administered, short-acting sympatheticomimetic amine, such as norepinephrine, whose pressor effect can be controlled promptly by regulating or shutting off the intravenous drip.[1] Because the pressor effect cannot be so closely controlled with intramuscular administration, extreme hypertension may result. Therefore, this route should be used only when the intravenous method is not convenient.

Hypometabolic treatment of cardiac arrhythmias

A. Recurrent tachycardias. Many patients with a normal metabolic state complain of recurrent episodes of supraventricular or ventricular tachycardia which cannot be controlled by the usual prophylactic measures, such as sedatives, quinidine, Pronestyl, and digitalis.[17] When a hypometabolic state was induced in a series of 39 such patients with antithyroid medications, such as propylthiouracil or radioactive iodine, the arrhythmias were eliminated in 33.[17] One of these patients had complained of recurrent supraventricular tachycardia for 36 years. The treatment resulted in complete relief from the attacks. In those treated with propylthiouracil, such a large dosage had to be used that leukopenia resulted. For this reason, radioactive iodine is to be preferred for the induction of a hypometabolic state. Very often when radioactive iodine is used, the metabolism is lowered to a myxedematous level. The patient then complains of disturbing symptoms, such as coldness, increased lacrimation, fatigue, gain in weight, and constipation. These symptoms can be corrected by administering very small doses of thyroid, such as 6 mg. per day. Larger dosage (30 to 60 mg.) is apt to cause a recurrence of the tachycardia.

One can but theorize why the induction of a hypometabolic state should prevent the recurrences of tachycardia. It is believed that the thyroid hormone does not affect the heart directly but has some indirect effect, either of increasing the work of the heart or of preventing the break-

every 10 to 15 minutes. The subcutaneous dose is 0.2 mg. every *45 to 60 minutes.* It may also be administered intravenously as a constant drip at a rate of 2 to 6 μg per minute. A minute-to-minute vigil must be maintained on the response, and the rate of administration adjusted to it.

Steroids have been reported to be effective in the treatment of heart block.[44] Because we have had no success with this treatment, we wonder whether many of the reported results are only fortuitous.[1]

Bellet and his group[24] have reported effective results with the use of molar lactate. Because serious cardiac arrhythmias may be induced by this treatment, it is necessary to carefully monitor the patient with an electrocardiogram during its administration. The dosage recommended was a variable one, from 15 c.c. of molar sodium lactate given intravenously in a few minutes to 960 c.c. over several hours. The rapidity and dose of injection depended upon the urgency of restoring the heart rate.

Prophylactic measures used to prevent further attacks include sublingual isoproterenol in doses of 15 to 30 mg. every 4 hours, or orally administered ephedrine sulfate, 25 to 50 mg. four times daily. A newer preparation, isoproterenol (Isuprel) in a sustaining media which allows slow release of the active agent, is possibly the most effective of the group.[40] Isoproterenol and epinephrine may also be injected intramuscularly once or twice daily or used in a nebulizer spray. Atropine-like drugs are also effective in preventing Adams-Stokes attacks.

B. Electrical stimulation. Zoll[25] reported on the practical use of an external cardiac stimulator for maintaining the rhythmic beating of the heart. Since then, there have been a host of other reports which describe improved means of electrical stimulation using epicardial, myocardial, and endocardial electrodes.[26-28,31,32] Although the use of cardiac pacemakers has proved to be of great value, they have a practical limitation, in that within a few days to a few months they often cease to function. Particularly is this true of techniques employing an imbedded myocardial wire, which usually requires greater and greater voltage; then it fails to stimulate the heart after several weeks because of a fibrotic reaction and increased electrical resistance at the point of contact. Nevertheless, despite this limitation, cardiac pacemakers have proved to be of great value in the medical and surgical wards, and, more particularly, on the operating table to tide the patient over until A-V conduction is re-established. Lillehei has stated in this regard that with the use of cardiac pacemakers, "The mortality of heart block has fallen to near zero and this fact has been most important in reducing the overall risk for ventricular septal defect surgery to low levels."[23]

Cardiac arrest and the problem of resuscitation

Circulatory arrest is considered to have occurred when the heartbeat is no longer strong enough to be of hemodynamic significance. In a series of 132 cases of cardiac arrest which occurred in the operating rooms of hospitals in the Los Angeles area, 70 per cent of the cases were due to ventricular standstill.[30] If the patient was resuscitated after a 4-minute period, cerebral damage was so marked that he remained in a vegetative state for the rest of his life.

The closed-chest technique of resuscitation should be instituted immediately when arrest is suspected. The problem arises when closed-chest procedure fails—should the physician attempt to resuscitate the patient by open-chest techniques? What is the moral and legal obligation of the physician to patients who have suffered from cardiac arrest? Who should be resuscitated and who not? A patient with metastatic malignant disease or one with a long history of severe intractable congestive heart failure presents a situation which is entirely different from that of a young healthy person who has arrest as a result of a diagnostic procedure.

The 4-minute time limit which was stressed in 1956 is a very important guide for the medical management.[30] If the circulation has ceased for a period of time longer than 4 minutes, and the closed-chest technique was omitted, resuscitation may only result in the production of a decerebrate state. It is then probably better that nothing be done under these circumstances.

ity. Since Levine and Lown[20] have demonstrated that the heart is more sensitive to digitalis during hypokalemia, it is evident that the first treatment after withdrawal of the digitalis should be the administration of potassium. There are many forms of therapy with potassium. It is best administered in solution orally, or intravenously. The absorption of enteric-coated tablets is unreliable.

The chelating agent, trisodium ethylenediaminetetraäcetic acid (EDTA), appears to be very effective in the treatment of digitalis toxicity.[1,21] EDTA depresses the level of ionizable calcium in the serum and this renders the heart less sensitive to digitalis. It has long been known that if calcium is administered to patients who have been digitalized on a tolerable dose of digitalis, serious arrhythmias may occur because of what we might classify as digitalis toxicity. Conversely, if the serum calcium is reduced in the patient with digitalis toxicity, the heart becomes less sensitive to digitalis and will revert to normal rhythm. Various digitalis-induced arrhythmias, such as ventricular and supraventricular arrhythmias, can be promptly abolished by the intravenous use of EDTA. Its action is faster than that of potassium given orally. When the A-V conduction is affected, EDTA is safer than intravenous potassium because of the depressant action of the latter on the heart muscle. Up to 3.0 Gm. of EDTA is usually sufficient to correct arrhythmias, but, in many of our experimental animals, we have noted that the original arrhythmia recurred within 20 minutes. EDTA should then be readministered. It was believed that EDTA had a specific action, in that it only corrected digitalis-induced arrhythmias. Recent evidence indicates that it also may correct arrhythmias of other etiology and, therefore, should not be considered as a specific test for digitalis toxicity.

Magnesium, Dilantin, procaine amide (Pronestyl), or quinidine have also been found to be effective in the treatment of digitalis-induced arrhythmias. However, if conduction defects have resulted from depression of the myocardium, Pronestyl or quinidine may aggravate the condition because of increased block. Recent studies by Brill[22] indicate that vasopressor drugs may also correct digitalis-induced arrhythmias.

Management of complete heart block

The clinical course and life expectancy of patients with complete heart block is an unpredictable one. Penton and associates[23] reported that the duration of life after the first appearance of heart block averaged about 2 years. They also reported a 42 per cent immediate mortality when complete heart block occurred after an acute coronary occlusion.

It is not necessary to treat the patient with acute incomplete or complete heart block unless symptoms such as dizziness, syncope, angina, or congestive failure result. There are now several methods of treating complete heart block; these can be divided into pharmacological or electrical. In evaluating the efficacy of treatment, the observer must remember that, in most instances, heart block returns to normal conduction spontaneously.[1,27]

A. Pharmacological methods. Sympatheticomimetic amines have a potent effect on the rhythmic function of the heart and may also improve conduction through the A-V system. Epinephrine, ephedrine, Paredrine, and isopropylnorepinephrine (Isuprel) are often effective in establishing a normal conduction or in speeding up an idioventricular rhythm. These amines, however, may also induce such serious ventricular arrhythmias as ventricular tachycardia and fibrillation.[1,24] Atropine and other drugs which block the vagus nerve have proved to be of value in certain cases of heart block in which vagotonia plays a significant role.

When heroic measures are indicated for an acute attack of Adams-Stokes syncope, or when the effective circulation has ceased because of heart block, epinephrine should be administered immediately by intracardiac injection. If there is still a peripheral circulation, the epinephrine may be administered intravenously at frequent intervals or by a constant intravenous drip. For a slower acting but more prolonged effect, a subcutaneous injection of epinephrine in oil may be employed. For grave emergencies, Isuprel may be given by intracardiac injection and repeated

stored blood will increase the extracellular content of potassium. Hyperpotassemia results and may cause cardiac arrest.[1]

Diphenylhydantoin (Dilantin) sodium

Recent experimental studies[39] indicate that diphenylhydantoin (Dilantin) sodium is effective for the treatment of atrial flutter and fibrillation and ventricular tachycardia. Experimental cardiac arrhythmias induced by locally applied aconitine or delphinine could be terminated by intravenously administered Dilantin. The effect was often temporary, but readministration of the Dilantin was again effective. Administration of intravenous diphenylhydantoin sodium corrected ventricular tachycardia in a patient after a myocardial infarction. The drug may be useful in the treatment of arrhythmias which arise from digitalis toxicity or which are secondary to myocardial infarction. The mode of action of the substance is unknown. We have also found that this drug will prevent recurrent paroxysms of atrial tachycardia or fibrillation.

2,6-Bis (1-piperidylmethyl)-4-(a,a-dimethylbenzyl) phenol dihydrobromide (Rhythmol)

Encouraging results have been reported[41,42] with a new drug, 2,6-bis (1-piperidylmethyl)-4-(a,a-dimethylbenzyl) phenol dihydrobromide (Rhythmol) (Ro 2-5803). It has been effectively used to treat ectopic atrial rhythms, such as paroxysmal atrial fibrillation and flutter. Atrial slowing as well as a decrease in the ventricular rate was apparent in almost all cases. A significant decrease or complete disappearance of premature ventricular systoles was obtained in 70 per cent of patients. A-V heart block has also been abolished after the use of the drug. It has been suggested that it may reverse arrhythmias which have been induced by digitalis.

Summary

1. In the case of cardiac arrhythmias, the need for treatment and its urgency must be weighed against the potential dangers of the treatment. This can best be carried out when the recent advances in pathophysiology and the clinical consequences of the arrhythmia are considered.

2. Vasopressor agents are effective in aborting arrhythmias or supporting the systemic pressure if hypotension results from the arrhythmia.

3. Induction of hypometabolism may prevent recurrent tachycardias and is also effective in slowing the rapid ventricular rate in drug-resistant, chronic atrial fibrillation.

4. Digitalis toxicity may be effectively corrected by the administration of potassium or of chelating agents which reduce the serum calcium.

5. Treatment of complete heart block by the use of the electrical stimulator is often temporarily successful, but permanent A-V conduction must be re-established within a few weeks or the chances of recovery are reduced.

6. The methods and indications for the treatment of cardiac arrest should be understood by all physicians, surgeons, and nursing staffs.

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For this reason, an accurate notation of the time at which either the heartbeat stopped or respirations ceased is vitally important.

First, consider those patients who suffer cardiac arrest in the hospital as a result of a procedure in the operating and delivery rooms, the cardiac catheterization laboratory, the emergency ward, and the x-ray department. Many of these instances may be termed "iatrogenic arrest," because they have occurred as the result of some mode of therapy or diagnostic test.[1] Anaphylactic shock, intravenous medications, induction of anesthesia, or the injection of contrast media for radiographic purposes are some examples of causes of iatrogenic cardiac arrest. Patients on the medical wards who die because they have suffered a small coronary occlusion, although they have an otherwise healthy body and sound mind, have been considered to have "hearts too good to die."[32] There is no doubt that an attempt should be made to resuscitate this type of patient. If closed-chest resuscitation fails, open-chest techniques should be instituted immediately. In the operating room of the hospital, the appropriate and necessary facilities for open-chest resuscitation are close at hand. Trained help, airways, instruments, drugs, equipment for monitoring the patient, defibrillators, and pacemakers should always be available for such emergencies. Certain departments in the hospital, such as the catheterization unit, should have a ready and immediately accessible kit which contains the required equipment.

Instances of cardiac arrest which occur outside the hospital pose a different problem. These are cases which occur in the physician's office or in the home, cases due to accidental electrocutions, and some cases of drowning. The following questions must be quickly answered: (1) Has the 4-minute time limit been exceeded? (2) Is the necessary help and equipment available? (3) Is the patient salvageable? Few physicians will have the opportunity or the need to consider these questions because only seldom will they be present within the critical time limit of 4 minutes. When the physician has decided to attempt resuscitation, what is the next step? First, an accurate notation of the time must be made. Secondly, an adequate, clear airway must be established and artificial respiration carried out either by endotracheal intubation with insufflation of oxygen or by mouth-to-mouth breathing. Once respiration is being carried out, the next step is manual compression over the sternum.[35] Thumping the chest or needling of the heart probably does little to restore the cardiac action and wastes precious time,[33] as does taking an electrocardiogram or the blood pressure. If the closed-chest technique fails, immediate thoracotomy with massage of the heart and the judicious use of intracardiac drugs, such as Adrenalin or procaine, and the use of the defibrillator are indicated. The heart must be massaged for at least 5 minutes before one stops to observe it. Recently, Hyman[34] has demonstrated that if the patient is packed in ice after resuscitation, cerebral damage is less likely to occur.

It is essential that every physician know the details and technique of open-chest and closed-chest cardiac massage. Classic detailed descriptions of the techniques have been reported by Kouwenhoven,[35] Beck,[32] and Hosler.[33]

Cardiac arrest due to blood transfusion

The repeated administration of blood transfusions may cause hypocalcemia, hyperpotassemia, and cardiac arrest. In each bottle of blood stored for transfusion there is an approximate 30 per cent excess citrate which will combine with the patient's ionizable calcium. One of the first signs of hypocalcemia is hypotension which is followed by bradycardia, which may lead to cardiac arrest. One or two transfusions of 500 c.c. each are generally innocuous, but if more is given, calcium must be administered to the patient to prevent hypocalcemia. Calcium gluconate, 0.5 Gm., should be administered for each 500 c.c. of blood transfused. The calcium gluconate should be injected intravenously in a vein other than that being used for the blood transfusion.

Citrate itself is toxic. Excretion of citrate from the body is impaired in shock states, and this will cause citrate toxicity.

Because red blood cells contain much potassium, the breakdown of the cells in

Annotations

Is there a decreased incidence of myocardial infarction in patients with cirrhosis of the liver?

The relationship of alcohol to atheroma continues to be disputed. Indeed, there is an impression among some clinicians that alcoholics are less liable to atheroma and its consequences than is the general population. Several attempts have recently been made to study this problem objectively. Three groups of workers[1-3] have studied the incidence of myocardial infarction found at necropsy in subjects with cirrhosis of the liver. In one of these studies a matched control group of necropsy subjects was employed.[3] All three investigations showed that the frequency of myocardial infarction in subjects with cirrhosis at necropsy was about a quarter of that in patients without hepatic cirrhosis.

There has been much speculation as to the possible causes of this rarity of myocardial infarction among patients with hepatic cirrhosis. It has been suggested that the diet of alcoholics lacks atherogenic substances or that the alcoholic liver cannot manufacture cholesterol.[4] A different speculation, namely, that hepatic cirrhosis may protect against myocardial infarction by increasing fibrinolysis,[5] has also been put forward.[2] Finally, Raaschou[6] has suggested that the low incidence of myocardial infarction in cirrhotic patients may be related to the infrequency of hypertension[7,8] among this group.

Before discussing biologic factors which might be responsible for the rarity of myocardial infarction among cirrhotic patients, one should question the statistical assumptions made in studies based on necropsy data.[9] Cornfield[10] has shown that, even if two lethal diseases have no relationship in a living population, there will nevertheless be a negative association between them in a necropsy study. Therefore, it is to be expected that, at necropsy, myocardial infarction (a fatal disease) would be relatively rare among subjects with cirrhosis of the liver (a second fatal disease). Similarly, the low frequency of extrahepatic cancer, and particularly of metastasizing carcinoma, among patients with cirrhosis of the liver may well be due to such statistical selection.[11]

The high mortality of cirrhosis could cause a reduction in the incidence of myocardial infarction of the observed magnitude.[11] The rarity, at necropsy, of myocardial infarction in this group might be due, therefore, to the high mortality of cirrhosis rather than to a low frequency of myocardial infarction among cirrhotic patients. An inevitable bias of postmortem studies seems to have produced an artificial statistical correlation which may not be valid in a living population. These statistical considerations certainly cannot disprove a possible relationship between cirrhosis and myocardial infarction. However, they do show that it is hard for retrospective necropsy studies to prove a negative correlation between two diseases even if matched controls are used. Prospective clinical investigations and experimental work appear to be much better adapted to a solution of this interesting problem.

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are pathognomonic, but the diagnosis should be considered in any case of cardiac failure in which one of the common causes of heart disease cannot be readily established.[1] Often the clue to correct diagnosis is the presence of multisystem disease, since involvement is rarely confined solely to the heart. Occasionally, a striking physical sign may be of aid, such as macroglossia, purpura with or without visible skin infiltration, periarteriolar deposits in the ocular fundi, or vitreous opacities.

The impression that cardiac amyloidosis is present in a patient with obscure heart disease who otherwise is known or suspected to have amyloidosis may be strengthened by a number of findings such as those observed in the previous two cases. Salient points are as follows:

First, congestive failure which is intractable even to vigorous treatment has frequently been noted.[3] Myocardial involvement is responsible for most of the observed hemodynamic effects, but valvular or pulmonary infiltration may, on occasion, be important. Amyloid deposition within coronary vessels which results in narrowed lumen or actual thrombosis is infrequent, and gross infarction is rare.

Second, a syndrome may be present which is virtually indistinguishable from chronic restrictive pericarditis.[4] There may be a history of dyspnea without orthopnea. The heart may be either normal in size or enlarged; other physical findings may include parasternal systolic retraction, protodiastolic extra sound, high venous pressure with dilation of neck veins, hypotension and narrow pulse base line, paradoxical pulse, enlarged and tender liver, anasarca, and cyanosis. Cardiac pulsations of low magnitude may be seen during fluoroscopic examination. On cardiac catheterization the pressure curves reflect restriction of normal ventricular filling. The end-diastolic pressure in the right ventricle is characteristically increased to more than a third of the peak systolic pressure, and there is a high diastolic pressure plateau with an early diastolic dip.

Third, electrocardiographic abnormalities are common, although the changes are nonspecific.[5] Characteristically, the QRS complexes are of low voltage and may be notched or prolonged. Especially in the precordial leads there may be loss of R wave over an area of discrete amyloid infiltration, which may suggest myocardial infarction. Inverted, diphasic, or low T waves may be present in the standard leads and in the left chest leads. Atrioventricular block and disordered rhythm, especially atrial fibrillation, are frequently seen.

Fourth, sensitivity to the cardiotoxic actions of digitalis was noted in the two cases presented. The occurrence of similar block or arrhythmia[6] with amounts of digitalis not generally regarded as excessive has also been noted in aged or debilitated patients, as well as in those with advanced heart disease, hypokalemia and electrolyte disturbances, severe pulmonary, hepatic, or renal insufficiency, myxedema, acute myocardial infarction, rheumatic or viral myocarditis, and endocardial fibroelastosis. In these two cases, toxicity was thought to result chiefly from amyloid deposition within the heart. Experience indicates that such sensitivity is not present in all patients with cardiac amyloidosis or even in the majority. In suspected cases, however, it would seem advisable for the physician to administer digitalis with even more caution than usual. Likewise, cardiac amyloidosis might be suspected if digitalis sensitivity is manifested in a case of otherwise unexplained heart disease.

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Muscular subvalvular aortic stenosis

Hypertrophy of the musculature of the left ventricular outflow tract is becoming a well-recognized variant of subvalvular aortic stenosis. The thickened muscle of the interventricular septum and the anterior left ventricle come together during ventricular systole, narrowing the outflow area and impeding ventricular ejection.

In a review of the clinical, hemodynamic, and pathologic features of 8 patients with this disease, we have attempted to elucidate further some of the diagnostic criteria.

Previous reports and the majority of patients in our series indicate that, most commonly, muscular obstruction of the left ventricle becomes clinically apparent between the second and fourth decades. However, both children and older patients with this disease have been described. Frequently a family history of a similar form of heart disease

Letters to the Editor

Guy's Hospital
London, England
March 16, 1962

To the Editor:

In the paper on aortic atresia published by Elliott and associates,[1] the authors say (page 826) that in their case "the coronary arteries were normally situated, although transposition of these vessels has been reported in cases of aortic atresia," and then at this point quote my paper on the same subject.[2]

As the Spanish text of my paper has clearly been misunderstood, I should like to make it clear that the coronary anomaly present in my case was the independent origin of the three main branches of the left coronary artery from the aorta. I said literally that "this anomaly is different from the anomalous coronary distribution found in cases of partial or incomplete transposition."

To my knowledge, no case of aortic atresia with transposition of the coronary arteries has been published. This is an important point, because should such an association exist, then we would have to consider aortic atresia as being related to some form of a transposition of the great vessels.

A. Sánchez-Cascos, M.D.
Cardiac Research Worker

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The Charles T. Miller Hospital
125 West College Avenue
Saint Paul 2, Minn.
April 11, 1962

To the Editor:

Thank you for your recent letter bringing to my attention the error in Spanish interpretation in regard to the origin and pattern of the coronary arteries in aortic atresia as discussed by Sánchez-Cascos.

This is always a real problem when one attempts to review the world literature.

Thank you very much for calling this to my attention.

Larry P. Elliott, M.D.

be elicited. Presenting symptoms include dyspnea, fatigue, angina, lightheadedness, and palpitations. Congestive heart failure may occur and sudden death is not uncommon. A systolic thrill and harsh "diamond-shaped" systolic murmur are present along the lower left sternal border. Rarely, the thrill is felt better in the suprasternal notch. Transmission of the murmur to the vessels of the neck occurred in half of the patients in our study, although other reports suggest that this is uncommon. The murmur may have a higher pitched component and, frequently, mitral insufficiency is suspected. The presence of a diastolic murmur would make the diagnosis of muscular obstruction of the outflow tract unlikely The second sound in the aortic area is usually of normal intensity, and an ejection click is not audible Some reports indicate that paradoxical splitting of the second sound occurs frequently, but this phenomenon could not be demonstrated in any of our cases. Apical third and fourth sounds may be detected.

Both roentgenograms and electrocardiograms disclose marked left ventricular hypertrophy and, not uncommonly, left atrial enlargement. Absence of calcification of the aortic valve and dilatation of the ascending aorta as evidenced by x-ray examination are helpful diagnostic aids in distinguishing this disease from valvular aortic stenosis In many cases a narrowed outflow tract can readily be demonstrated by angiocardiography.

Four hemodynamic findings are fairly specific for muscular obstruction of the left ventricular outflow tract.

1 An infundibular pressure zone. As the catheter is withdrawn from the left ventricle to the aorta, a reduction in systolic pressure with unchanged diastolic pressures is noted in the outflow area As the aortic valve is traversed, the systolic pressure remains unaltered, but the diastolic pressure rises to systemic levels.

2 Anacrotic notch on the left ventricular pressure curve Initial systolic ejection is unimpeded. However, as the thickened muscle becomes approximated, there is temporary obstruction until a higher left ventricular pressure can overcome this "functional" impairment. This results in the temporary delay on the upstroke of the ventricular pressure curve.

3. Bisferious aortic pulse. Patients with muscular obstruction demonstrate a rapid systolic upstroke, unlike the prolonged ascent of the central arterial pulse of patients with aortic stenosis. Commonly, the aortic curve has a secondary peak or "tidal wave." The sharp systolic upsweep and initial peak occur with early systolic contraction. Obstruction (with the resulting trough) follows and then the delayed ejection of blood which causes the secondary or tidal form.

4. Small compensatory beat after extrasystoles. After an extrasystole and compensatory pause the ventricle contracts with greater force so that the musculature of the outflow tract becomes more tightly approximated and produces an increase in the functional stenosis. As a result of the more severe obstruction, the ventricular pressure in the compensatory beat rises, whereas the pulse pressure in the aortic curve is smaller. The reduced amplitude of the aortic pulse is in contradistinction to that of the normal heart, wherein one would anticipate a larger pulse pressure in the compensatory beat.

Additional hemodynamic findings include pulsus alternans, an elevated pulmonary arterial pressure, left atrial contraction waves, and an elevated end-diastolic pressure in the left ventricle.

Not uncommonly, anesthesia with a resultant decrease in cardiac output may diminish or completely abolish the gradient in the outflow tract. In addition, incompetence or stenosis of the mitral valve may be apparent and probably results both from distortion of the mitral orifice by the grossly thickened musculature and from the high end-diastolic left ventricular pressures.

At autopsy the hearts are tremendously enlarged. In order to establish pathologic criteria for the diagnosis of muscular subvalvular stenosis, the interventricular septum was sectioned vertically and the width 1 5 cm down from the junction of the muscular and membranous septum was measured. The septal width was divided by the thickness of the left ventricle in an attempt to establish a ratio between the two. Similar evaluation was made of 50 hypertrophied and 20 apparently normal hearts. The septal to ventricular ratio exceeded 1.5 in each of the hearts with muscular obstruction, whereas in the control hearts it averaged 1. We concluded that, if at the time of necropsy this ratio exceeds 1.3, the presence of obstruction to left ventricular ejection prior to death should be suspected. In each instance there was also marked endocardial fibrosis in the outflow tract of the left ventricle. Microscopic sections of the septum in the area of obstruction demonstrated little alteration in the myocardium as compared to the control hearts

The etiology of this disease remains obscure. Previous reports in children, as well as several unreported cases of our own, indicate that it may be of congenital origin. Although there appears to be a significant familial incidence, positive conclusions in regard to etiology cannot be drawn at this time.

Hermann Menges, Jr., M.D.
University Hospitals of Cleveland
Cleveland, Ohio

(Baschieri, L. de Caro), the United States (Bing), Switzerland (Hegglin), Sweden (Carlsten and associates, Többis and Söderberg), Belgium (Leusen and Lacroix), England (Peel and associates), Bulgaria (Orahovats and associates), in addition to several authors from Austria. In contrast, no papers were presented by East German authors.

The definition of heart metabolism is fairly broad and includes relationship of metabolic changes to structure (studied with the electron microscope by F. Büchner, p. 125), to ion transport (G. Rudolph, p. 93) and electrolyte changes (Nieper and Blumberger, p. 238), to cardiac oxygen consumption and coronary blood flow (H. J. Bretschneider, p. 32), and to cardiac work. The results presented are based on detailed chemical analysis of the heart muscle in animal experiments as well as catheterization of the coronary sinus in man (K. G. Bing, p. 145, Bernsmeier and Rudolph, p. 59). Changes of heart metabolism in experimental hypoxia, in exercise, and in various pathologic conditions (cardiac decompensation, coronary insufficiency and myocardial infarction, diabetes, etc.) are discussed in detail. Among the main reviews were those presented by W. Lamprecht (Metabolism, Energetics, and Regulatory Mechanisms, pp. 3-31), H. J. Bretschneider (Cardiac Oxygen Demand and Supply, pp. 33-58), A. Bernsmeier and W. Rudolph (Myocardial Metabolism, pp. 59-75), W. Thorn (Metabolites in Heart Muscle in Normal Conditions, Hypoxia and Anoxia, pp. 76-89), G. Rudolph (Transport and Effect of Ions, pp 93-112), R. J. Bing (Metabolism of the Intact Heart, pp. 145-166), R. Hegglin (Clinical Problems of Myocardial Metabolism, pp. 175-188), and H. Lüllmann (Effects of Drugs on Elementary Processes in the Heart, pp. 277-284). This arbitrary selection of papers may suffice to show the variety of important aspects covered in this volume. The bibliography in these and other reviews is extensive.

Several papers, presented on the last day of the meeting, are not directly related to the main topic. Of interest is the application of Hensel's *Wärmeleitsonde* (measurement of heat conduction from heated thermocouples at the tip of thin needles) (Betz, Braasch and Hensel, p. 321) to myocardial circulation. The needles were inserted into different parts of the myocardium, supplied by different branches of coronary arteries, so that the myocardial circulation in different myocardial regions could be recorded simultaneously. Of potential interest for clinical application is the reported favorable effect of ATP on stroke volume, mechanical work of the heart, and speed of contraction in hypodynamic hearts of rabbits (W. Gebhardt, p. 197). In view of the increasing diversification and complexity of medical research, Wezler's general considerations in his opening address are well worth reading.

The volume can be recommended without reservation to all students of cardiac physiology and pathology.

Bibliography of Medical Reviews Vol. 6: Cumulation, 1955-1961. National Library of Medicine, U. S. Department of Health, Education and Welfare. Washington, 1961, U. S. Government Printing Office, 436 pages. Price $3.50.

This book reflects a tremendous task. As noted in the introduction, it is estimated that the cumulation contains some 21,000 subject entries for approximately 13,500 review articles collected from 1,949 journal titles over a period of 6 years. It should be of obvious value.

Announcements

Training in Pediatric Cardiology. The Division of Cardiology, Department of Pediatrics, University of California at Los Angeles, is now accepting applications for training in pediatric cardiology beginning July, 1963. The traineeship is offered in cooperation with other clinical and preclinical departments of the UCLA School of Medicine for individuals interested in careers in this area. It includes instruction in all of the various aspects of both clinical and basic science pertinent to the practice and teaching of pediatric cardiology.

This 2- or 3-year interdisciplinary program is certified by the Board of Pediatric Cardiology. Instruction in clinical cardiology includes care of the patient, electrocardiography, phonocardiography, vectorcardiography, cardiac catheterization, angiocardiography, indicator-dilution methods, pulmonary physiology, and other techniques useful in the study of clinical cardiovascular problems. Instruction in basic cardiology includes physiology, biophysics, biostatistics, biochemistry, nuclear physics, and medical writing, as these relate to cardiology. Research is also required, and each trainee is encouraged to work toward the Master of Science degree in a related basic field of his choice.

Facilities. The Department of Pediatrics is part of a combined University Medical School and Hospital unit. The Hospital has 508 beds, of which 125 are for infants and children. Approximately

Book reviews

THERAPIE DER HERZKRANKHEITEN (Verhandlungen der Deutschen Gesellschaft fur Kreislaufforschung. 26 Tagung zu Bad Nauheim). Edited by Dr. Rudolf Thauer, Darmstadt, 1960, Dr. Dietrich Steinkopff Verlag.

Each year the German Society for Circulation Research holds a meeting, at which papers are presented and discussed. At each of these meetings, one or two main themes are selected for special emphasis, and the proceedings are published in book form. In 1960, the special topic for discussion was the therapy of heart disease interpreted broadly.

The subjects discussed included: digitalis glycosides, diuretic agents, anticoagulants, corticosteroids, antibiotics, rhythm disturbances, and coronary vasodilator agents. Altogether, this volume contains 32 individual presentations dealing with the main theme, as well as 9 others.

The large number of presentations imposes brevity on each and makes it difficult for any to be comprehensive. This practice contrasts with that observed a few years ago when the Society discussed cor pulmonale and coronary artery disease. In that instance the communications were detailed enough to give the published proceedings more lasting value as a reference work, for "outsiders." However, the proceedings of the 1960 meeting do give the English-speaking cardiologist a good view of current German thinking and practice.

Of special interest to the reviewer was the presentation of the Arthur Weber prize to Dr. H. J. Bretschneider for his work on sudden cardiac death. This investigator has apparently found evidence to support the existence of intracardiac nervous receptors which are a codeterminant of coronary blood flow. This work excites one's fancy, and it would have been interesting to have had it reported in the annual volume of the Society.

DISTURBANCES OF HEART RATE, RHYTHM AND CONDUCTION. By Eliot Corday, M.D., F.A.C.P., F.A.C.C., Assistant Clinical Professor of Medicine, University of California School of Medicine; and David W. Irving, M.D., Clinical Assistant, University of California School of Medicine. Philadelphia, 1961, W. B. Saunders Company, 357 pages. Price $8.50.

This book attempts to present, in a simple and concise manner, fundamentals extracted from the controversial and sometimes confusing field of cardiac mechanism disturbances. These fundamentals embody basic mechanisms, etiology, pathophysiology, hemodynamics, symptoms, physical signs, treatment, and prognosis of the disturbances in heart rate, rhythm, and conduction. A goal such as this is an admirable one, but the real value of such a presentation is ultimately determined by the audience to which it is directed.

This book can be recommended highly to the medical student, intern, resident, general practitioner, and internist. Although the material here is generally available in accepted texts on cardiology and in popular recent medical journals, its collection in a single source with a central theme is particularly useful. For the cardiologist, however, this reviewer believes that the contents are oversimplified and not of specific value where extensive data are needed. What is desirable for clinicians in this group are comprehensive guidelines to the approach of problems which arise in the diagnosis and treatment of mechanism disturbances. Here one is not satisfied with categorical statements, for seldom are the problems uncomplicated. Frequently, for example, one is more concerned with *when* auricular fibrillation or flutter should be converted rather than *how* this might be achieved. Many factors, including the etiology, type of heart lesion, duration of the mechanism disturbance, size of the cardiac chambers, effectiveness of digitalis control, presence of embolic episodes and many others, influence decisions relative to management. Specific situations need special consideration—for example, auricular fibrillation in association with thyrotoxicosis, or that which occurs after a recent myocardial infarction or in individuals who are potential candidates for surgical correction of acquired valvular defects. The question of anticoagulant therapy before, during, and after attempts at conversion requires careful thought. Decisions must be tempered by many factors, including the presence of cerebral emboli and the possibility of future cardiac surgery. The problems are immense and simplification is not possible. Detailed discussions of these problems will not be found in this or any other small book not intended to be a complete source of reference information.

It is not intended that the foregoing comments on a portion of this monograph detract from its over-all basic value. They are stated merely to orient the reader partially to what he might expect. This reviewer considers this a fine book and a valuable contribution if judged in the light of the reader-level for which it is apparently intended.

STOFFWECHSEL DES HERZMUSKELS (Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. 27 Tagung, April 7-9, 1961). Darmstadt, 1961, Dr. Dietrich Steinkopff Verlag, 355 pages.

Professor Dr. K. Wezler, the chairman of the meeting, suggested heart muscle metabolism as the main topic for the first time in the long history of the Deutsche Gesellschaft für Kreislaufforschung. The volume more than justifies Wezler's suggestion; there is a wealth of up-to-date information about heart metabolism presented in 35 papers, and subsequent discussions. Although most of the authors were German, there was some international flavor, with participants from Italy

American Heart Journal

August, 1962, Volume 64, Number 2

Editorial

Which leads shall we take?

William Evans, M.D.
London, England

There is no need to extol the virtues of the electrocardiograph as an aid to the diagnosis of heart disease; it has proved its worth. It helps, and never hinders nor confuses, a true appreciation of the heart's conduct. Should it at any time appear to give false testimony, the fault will be found to rest with the observer's interpretation of the tracing, and not with the information conveyed graphically in the course of the test.

The need of the moment is to look back over 70 years of clinical electrocardiography, to discover whether we now avail ourselves fully of the advantages which this test offers for the readier detection of abnormalities, both great and small, that affect the myocardium. A prelude to such scrutiny must necessarily be a brief account of the progressive steps taken by this science since its introduction, so that we may examine anew the reasons why certain recommendations that concern the selection of leads, and the positioning of electrodes, were accepted by practicing cardiologists.

Historical background

It may be said that some four milestones mark the progress of clinical electrocardiography. Naturally, the *first* was the recording by Waller[9] of the variations in the electrical potential occasioned by the heart's action. After Waller's brilliant researches, and subsequently those of Einthoven,[4] the three bipolar limb leads came into use. The *second* landmark was staked by Wolferth and Wood[12] when they wrote of the help given to the diagnosis of cardiac infarction through the employment of a chest lead. The *third* milestone is associated with the setting up of a committee formed of members of the American Heart Association and of the Cardiac Society of Great Britain and Ireland, which, when it met in 1938, made recommendations on the routine use of a single precordial lead. It suggested that in the case of this fourth lead, the exploring electrode over the apex beat should be paired with the indifferent electrode on the right arm, the left leg, or the left arm. Another recommendation of this committee was that in the case of all leads in which one electrode was placed much closer to the heart than the other, the galvanometer connections should be so arranged that relative positivity of the apical electrode should be represented in the finished curve by an upright deflection, and relative negativity by a downward deflection. The *fourth* landmark in the history of electrocardiography

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Editor's Note: This paper represents the opinion of the author, but it would be interesting to learn by letter the reaction of our readers.

pitalized for diagnosis, treatment, or study of heart disease. Cardiac patients are seen on an outpatient basis three times weekly.

The main teaching and research facilities are located in the newly constructed four-story Marion Davies Children's Wing. One entire floor of this structure is devoted to pediatric cardiology. It contains the pediatric catheterization laboratory, the cardiopulmonary laboratory, the chemistry laboratory, four research laboratories, a conference room, and offices for the trainees and full-time staff. Laboratories for surgical research are also located on this floor.

Staff. The Division of Cardiology is headed by Forrest H. Adams, M.D., and is staffed by five full-time, plus several part-time, cardiologists. Six of the staff are certified by the Board of Pediatric Cardiology. The research and technical staff consists of six medical technicians, two registered nurses, one x-ray technician, and one electronics technician.

Qualifications and stipend. The program is limited to graduates of medical schools in the United States or Canada. Candidates must have an M.D. degree and, in general, must have completed 2 years of graduate training in clinical pediatrics. Candidates who have had 1 year or more of training in pediatric cardiology in a recognized center may enroll for only 1 year. The stipend is $6,000.00 per year. Interested applicants should write to Arthur J. Moss, M.D., Cardiology Training Program Director, Department of Pediatrics, University of California, Los Angeles 24, Calif.

The International Society of Cardiology Foundation announces the availability of small awards for the support of research in the pathophysiology of the circulation. Awards are limited to a term of one year.

Individuals who wish to request support should direct inquiries to The International Society of Cardiology Foundation, 44 East 23rd St., New York 10, N. Y., U.S.A.

The IV World Congress of Cardiology will be held in Mexico City, October 7 through 13, 1962. Information on how to take an active part in the Congress follows:

Presentation of individual papers. Papers must be submitted through the national cardiological societies. Ten minutes will be allowed for a reading of the paper, and 5 minutes more for discussion of it. An abstract of it in three languages will be published in the final Program. At the time of its reading, it will be broadcast in the two other official languages, and it will be published in the Proceedings of the Congress.

Graphic exposition of original work. Some 600 square meters of floor space and adequate units are available for exhibition of original work in an attractive form during the Congress. Illustrative material, photographs, and special graphics which are submitted will be assembled properly by those in charge of the exhibits. Applicable rules will be sent upon request.

Collaboration in an institution paper. Such a paper will be presented by one of the authors, who will be entitled to 20 minutes for a reading of it, and 10 minutes more for discussion of it. Such a paper must sum up the work carried on by an important number of different specialists.

Participation in a meeting for coordinated discussion. The board will be composed of a Coordinating President and speakers. The discussion will be open, and those who desire to participate should contact the Coordinator of the meeting.

General conditions for writing up scientific contributions:

1. The common aim of all works must be to integrate the field of cardiology: most of the members of the Congress will be general cardiologists.
2. Abstracts must not exceed 200 words each.
3. Individual papers should have a maximum length of 3 typewritten sheets, double spaced, with 80 strokes per line and 35 lines per page. For publication in the Proceedings, 2 more sheets are allowed, without including bibliography, footnotes, and illustrations.
4. Abstracts and original papers which are to be read must be written in the three official languages of the Congress.
5. Illustrations and graphs must not be larger than 13 by 18 centimeters, and they must be of good enough quality to make perfect engravings. The word *Base* should be written on the reverse side of the material to indicate its correct position.
6. The bibliography should be written up in accordance with the international rules which are detailed in the provisional program of the Congress.
7. The name of the author and the title of the paper must be written on the reverse side of all pages and illustrations.

Registration fee. The registration fee for the Congress is $40 (U.S.) for active members, and $20 (U.S.) for associate members. To avoid serious difficulties, all hotel reservations should be made through the Secretariat of the Congress, Avenida Cuauhtemoc 300, Mexico 7, D.F., either directly or through its official travel agencies, Mundus Tours de Mexico and Viajes Internacionales Pegaso, Post Office Box 9170, Mexico, D.F.

National Survey of Prothrombin announced by the College of American Pathologists. The therapeutic benefit from the widespread use of anticoagulant medication makes it imperative that prothrombin measurements be reproducible and that similar levels be used consistently in this country. In order to stimulate interest in the accuracy and precision of prothrombin measurements, the College of American Pathologists will conduct a national survey.

Those who wish to participate in the prothrombin survey may do so by applying to the Committee for Clinical Pathology Standards, College of American Pathologists, Prudential Plaza, Chicago 1, Ill. In addition to the survey samples, a critique on prothrombin measurements containing suggestions for increasing the reproducibility and accuracy will be sent to each participant.

shown that this effect of the heart's lie on Lead III may be corrected by recording Lead IIIR; the same correction has to be applied to Lead V_F by recording it during deep inspiration (V_FR).

Moreover, the notion that the heart rotates in one or another direction in various diseases of the heart has arisen in electrocardiographic literature, often without anatomic basis, as judged by radiologic examination.

Again, the contour of the waves written in the three "unipolar" leads, V_R, V_L, and V_F, is not essentially different from that of the waves written in the three bipolar limb leads, except for Lead V_R, in which the tracing emphasizes the negativity of the primary waves instead of their positivity as in Lead I. The deliberate introduction of this distortion has always caused surprise, in that it was done in the face of special emphasis given by the Committee of the American Heart Association and the Cardiac Society of Great Britain and Ireland,[1] of which F. N. Wilson was a member, to the advantages gained by adopting a system which would ensure that an upright T wave was invariably normal irrespective of the lead producing it. This contorted Lead V_R has consequently mystified many, and doubtless mesmerized some into thinking that this was some new concept in electrocardiography to be adopted out of hand. It should be known for what it is, namely, a lead hardly different from the bipolar Lead I *turned upside down.*

Thus, the addition of the so-called "unipolar" limb leads to the four bipolar leads has contributed no single advantage to the diagnosis of heart disease, and they possess no virtue which justifies their inclusion in routine electrocardiography.

The chest leads. Although Waller had recorded chest leads in healthy subjects in 1889, their usefulness in the detection of heart disease was first advocated by Wolferth and Wood in 1932, and the intervening years have pronounced them to be indispensable.

Some discarded chest leads. The joint American and British Committee, considering the standardization of chest leads, recommended that the single precordial lead should be designated by the Roman numeral IV, and that its exploring electrode should be placed at the extreme outer border of the apex beat. Later, this lead was positioned in the fifth intercostal space in the left mid-clavicular line, irrespective of the place occupied by the apex beat. When more than one chest lead came into use, the term IV was changed to C (Chest). The committee suggested the pairing of this electrode with either the right arm (CR), the left arm (CL), or the left leg (CF). The CL lead found no favor in practice and was discarded early. The CF lead remained in use for some time, until it became clear that the influence of the electrical potential at the left leg frequently produced negativity of the T wave, depending on the lie of the heart, and so confused diagnosis; on this account the lead was also discarded. There remained the CR leads, which were in common use at a time when the "unipolar" leads were being introduced.

The relative merits of CR and V leads. Small wonder that V leads, which are now in common use, and which exemplify the "unipolar method" for electrocardiographic interpretation, have been subjected to criticism following their application in clinical practice, for they were introduced on *hypothetical* grounds. The initial adoption of "unipolar" leads rested on the false supposition that they were comparable with leads in direct contact with the exposed heart, recording principally the electrical events of that portion of the heart underlying and facing the electrode on the chest wall. It is now generally accepted that the tracing obtained in this way records the events happening in the heart as a whole.

The matching of V leads against other chest leads through *clinical trial* has not often taken place, for they were accepted out of hand in most clinics and without subjecting them to such probation. This has been an unfortunate fault and one which happens in the case of other products should their repute depend exclusively on laboratory assay. No lead, of course, gives an erroneous result, for they all act in concert with ordained electrophysical laws, but they differ greatly in the ease with which the tracings they produce can be interpreted clinically, and their ability to supply evidence that the heart is healthy or diseased. To the clinician in search of a bedside diagnosis it is this ...

is represented by the supplementary report submitted by the American members of the joint committee, who suggested six positions on the chest for the exploring electrode, and recommended that the precordial electrode should be paired with a central terminal connecting electrodes placed on the right arm (V_R), left arm (V_L), and left leg (V_F). Thus, was born "unipolar" electrocardiography.

Appraisal of leads and positioning of electrodes

The passing of time has enabled judgment to be passed on whether tenets propounded almost a quarter of a century ago have proved unassailable when applied to the clinical examination of patients through the intervening years. After all, many of the recommendations arose from conclusions drawn from experiments in the laboratory, and presumed to be in concert with the dictates of established electrophysical laws. Small wonder, therefore, if some of them have proved to be less useful in practice than such theoretical considerations predicted for them at the time.

In the review which follows, and which assesses the value of individual leads in the recognition of heart disease, and especially in the detection of small lesions within the myocardium, close attention is given to their ability to do this with the least expenditure of toil, where simplicity replaces complexity, but never through sacrificing accuracy for expediency.

The bipolar limb leads. The use of three bipolar limb leads over half a century has endorsed their usefulness, and accepted them as *standard* for all times. By themselves they make possible the diagnosis of the separate forms of irregularities of rhythm, facilitated by a relative prominence of the P wave in Lead II. The limb leads can also tell the presence of salient cardiac infarction. Indeed, when this considerable injury is limited to the postero-inferior and medial aspect of the left ventricle, the electrocardiographic changes may be confined to the limb leads, which show significant Q waves and depressed or inverted T waves in Leads II, and III and IIIR, whereas the chest leads may show no deformity. Moreover, although chest leads have to be added in the search for smaller myocardial lesions, in one instance in which the injury is limited to the anterolateral aspect of the left ventricle, changes are again confined to the limb leads when a deep S wave appears in Leads II and III in the absence of an S wave in Lead I.[2,3,10,11]

LEAD IIIR. When the heart assumes a transverse lie within a broad and shallow thorax or on account of an elevated diaphragm from any cause, Lead III may show a noticeable Q wave and inverted T wave, *conveying the impression of a myocardial injury*, but when the diaphragm is depressed during deep inspiration, a repeated tracing (Lead IIIR, where R stands for respiration) will show a shortening or disappearance of Q, and partial or complete correction of the deformed T wave and without depression of the S-T segment. Exceptionally, and in only some 5 per cent of the cases, this respiratory maneuver fails to effect this change; in such instances it will be found on x-ray screening that the diaphragm actually moves upward during inspiration.

This combination of Leads III and IIIR has proved to be a most valuable agent in the diagnosis of a limited cardiac infarction; it does this in two ways. First, should the S-T segment be depressed in IIIR when a lowering of the diaphragm has taken place during inspiration, and in the absence of both digitalization and the syndrome of the suspended heart,[5] cardiac infarction as the cause of chest pain is confirmed. Such S-T depression results from infarction affecting all segments of the left ventricle other than its anterior aspect. Secondly, and infrequently, should a Q wave, absent in Lead III appear in Lead IIIR, it is again evidence of a myocardial fault.

Thus, the recording of the four bipolar limb leads, I, II, III, and IIIR, forms an essential first phase of the electrocardiographic examination.

The "unipolar" limb leads. It is known that the lead which is least reliable in providing information about the state of heart muscle is the one connected to the left leg, as in Leads III and V_F, because of its sensitiveness to changes in the lie of the heart. Yet, in the "unipolar" leads this malinfluence is deliberately introduced into the arm leads through inclusion of the leg lead in the indifferent electrode formed by the common terminal.[10,11] It has already been

arm, are not hindered by this handicap. Leatham,[7] comparing CR, V, and CF leads in 100 healthy subjects, *found that neither* CR nor V leads held much practical advantage over each other *provided* that the normal pattern for each was known, although a T-wave inversion in Lead V_1 and rarely in Lead V_7 in healthy subjects was a disadvantage. The knowledge that the T wave may be inverted in Lead V_1 and even in Lead V_2 in the normal person does not, however, save one from making an error when chest *pain is being investigated*, for if this change happens alongside a small deformity of the T wave in Lead V_4, the *diagnosis of a small infarction may be* missed, whereas should the physiologic T *inversion in Leads* V_1 *and* V_2 *keep company* with obvious T inversion in Lead V_4, a wrong impression is gained of the size of the infarct, since it would be regarded as extensive. This explains Figure 2 in a paper by Herrmann and associates,[6] in which a limited injury, truly appraised in CR leads, is regarded as extensive by reference to V leads.

A greater handicap which results from the use of V leads is the low voltage of the tracing to the left of station 4, so that in practice it is *unsatisfactory to apply the* electrode beyond station 6. On the other hand, in the case of CR leads, a satisfactory tracing is always obtained in station 7 in the posterior axillary line, which contributes so materially to the diagnosis of early left ventricular hypertrophy and of cardiac infarction laterally disposed, and which shows changes in this station at an earlier stage than in station 6.

Again, the P or atrial wave is better displayed in CR chest leads than in V leads. Thus, Mounsey,[8] writing on the atrial electrocardiogram as a guide to prognosis after *mitral* valvotomy, used CR leads rather than V leads in the investigation, because the voltage of the P wave is greater in CR leads, permitting an estimate of right atrial activity represented by the first peak of the P wave in Lead CR_1, and of left atrial activity represented by the second peak of the P wave in Lead CR_7.

Similarly, this ability of Lead CR_1 to show the atrial wave to best advantage facilitates the electrocardiographic interpretation of certain examples of arrhythmia, demonstrating more clearly the degree of A-V dissociation in atrial tachycardia, or *the "f" waves in atrial fibrillation.*

The bipolar leads especially exert their superiority over "unipolar" leads in displaying the lesser electrocardiographic signs which tell of limited cardiac infarction at *the time in patients* with cardiac pain. Two of these are confined to bipolar limb leads, and the remaining seven appear mostly in the bipolar chest leads (Fig. 1). It is in this important field of cardiology that the recall *of CR leads into current practice is so* essential.

Naturally, Lead CR_4R is no substitute *for Lead* V_4R *as a means of telling right* ventricular hypertrophy, but this role is *adequately fulfilled by Leads* CR_1 *and* CR_2.

Positioning the electrode. Although many elect to record six chest leads, others employ only three. In "unipolar" electrocardiography these may be stations 2, 4, and 6. With bipolar leads, advantage, denied to V leads because of the small voltage, can be taken of station 7, whose merits in the diagnosis of early left ventricular hypertrophy and limited infarction in the lateral wall of the left ventricle have already been extolled. Three positions only are needed *for these CR leads, namely, 1, 4, and 7.* No abnormality is ever found in stations 2 and 3 that is not apparent in 1 or 4, nor in 5 and 6 that is absent in both 4 and 7; occasionally, Lead CR_2 is a useful addition should the R wave be absent in Lead CR_1.

Incidentally, the galvanometer connections needed for bipolar electrocardiography could be reduced to provide for only three leads, so that for the recording of CR leads the limb lead electrode remains on the right arm serving as the indifferent electrode, whereas the left arm electrode is used as the exploring electrode on the chest, and the lead switch is turned to Lead I.

Thus, in clinical cardiology, the bipolar CR leads have proved to be vastly superior to the "unipolar" leads, and three positions only on the chest give adequate information.

Vectorcardiography is never to supplant electrocardiography in clinical cardiology, for although it can facilitate the analysis of events taking place during the QRS phase, it does not display as clearly as the orthodox electrocardiogram the more cryptic cha...

AFFECTED PART OF ELECTROCARDIOGRAM	NATURE OF DEFORMITY	
	DESCRIBED	SCHEMATIC REPRESENTATION
Q WAVE	ABSENT in III and APPEARING in IIIR	III ⊕ IIIR
RS SEGMENT	NOTCHED RS_7	CR_1
S WAVE	DEEP in II and III (Absent in I)	II III
ST SEGMENT	SICKLE DEPRESSION(1) PLANE DEPRESSION(2)	⊛ 1 2
T WAVE	LOW in I and in CR_4 or CR_7	● I CR_4 or CR_7
	BLUNT	
	TERMINAL DIP	
TU SEGMENT	DEPRESSION	
U WAVE	INVERSION	

KEY
- ⊕ : Provided DIAPHRAGM IS DEPRESSED during deep inspiration
- ⊛ : Provided DIGITALIZATION is absent
- ● : Provided EXERCISE ELECTROCARDIOGRAM gives a positive reaction

Fig. 1. Diagrammatic representation of the lesser electrocardiographic deformities which arise from cardiac infarction of limited distribution.

matters most. Having adopted the principle that the normal T wave is invariably upright irrespective of the lead producing it (Committee of the American Heart Association and of the Cardiac Society of Great Britain and Ireland, 1938), one should judge the merits of a chest lead by its ability to demonstrate negativity of the T wave in the abnormal, and positivity in health. The V chest leads emphasize the negativity of T waves, although not to the same extent as CF leads, which were rejected for this reason. CR leads, on the other hand, with the indifferent electrode on the right

Clinical communications

The significance of aortic ejection systolic murmurs

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Accuracy in the diagnosis of heart disease has increased tremendously in the last decade, necessitated largely by the remarkable advances in cardiac surgery. Although cardiac catheterization and angiocardiography, together with improved methods of electrocardiography and phonocardiography, have made an exact diagnosis possible, clinical examination of the heart has also progressed and is still of major importance. The clinical assessment of an isolated systolic murmur remains perhaps the most common problem facing the modern cardiologist.

It is the purpose of this paper to review the problem of the recognition and significance of an aortic ejection systolic murmur in persons with little or no other evidence of heart disease. Bruns and van der Hauwaert[1] have shown that there is a high incidence of aortic systolic murmurs in normotensive middle-aged and elderly persons, and that minimal atherosclerotic thickening of the base of the valve cusp is the cause in the vast majority of instances. Barlow and Kincaid-Smith[2] found a high incidence of aortic systolic murmurs in hypertensive patients of all ages, although they believed that in these circumstances the aortic valve is often anatomically normal. For the purpose of this study, therefore, we have confined ourselves to normotensive patients under the age of 35 years.

Characteristics of aortic ejection systolic murmurs

The systolic murmur of aortic stenosis is usually heard at both apex and base and may be loudest at either area.[3,4] The murmur is transmitted up the carotid *arteries, especially on the right side,*[5] and is characteristically louder over these *vessels than in the adjacent tissues of the* neck. Aortic ejection systolic murmurs due to causes other than stenosis of the valve usually follow the same pattern, but phonocardiography shows that the murmur is shorter and the maximal accentuation earlier than in stenosis of the valve.[1,2,6]

Difficulty may sometimes arise when venous or arterial bruits are present in the neck. These may be transmitted to the precordium[7,8] and thus be difficult to distinguish from murmurs which arise at the aortic valve and radiate to the neck. The characteristic continuous murmur of a venous hum can usually be easily recognized[7]; but, when the patient is in the supine position, the diastolic component may disappear,[9] and, since it is best heard over the internal *jugular* vein in close proximity to the carotid artery,

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that take place in the S-T segment and the T wave.

Conclusion

The advantages at first canvassed for so-called "unipolar" electrocardiography, a method introduced into the field of cardiology on hypothetical grounds and accepted out of hand in the absence of a preliminary clinical trial involving its comparison with other leads, have not been confirmed.

Now that the lapse of time has provided ample opportunity to carry out such comparison, *the superiority of bipolar lead* electrocardiography has been established. Thus, the "unipolar" *limb* leads are redundant when recorded additional to the more informative bipolar limb leads, whereas the V *chest* leads have proved inferior to CR leads in every domain of clinical cardiology.

The seven leads requisite for general use consist of the four limb leads, I, II, III, and IIIR (Lead III during deep inspiration), and the three chest leads, CR_1, CR_4, *and* CR_7; *occasionally, the addition of* CR_2 *is an advantage.*

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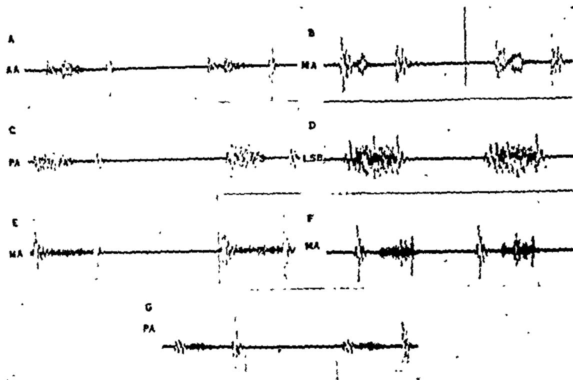


Fig. 1. Phonocardiograms, showing the seven different types of systolic murmurs which may be associated with a normal second heart sound, electrocardiogram, and roentgenogram. *A*, Short, crescendo-decrescendo aortic ejection murmur (Case 14, Table I) *B*, Regular, low-frequency vibrations of a "vibratory" murmur. *C*, Atypical, short, crescendo-decrescendo murmur of a very small ventricular septal defect. *D*, Typical pansystolic murmur of a small ventricular septal defect. *E*, Pansystolic murmur of mitral incompetence. *F*, Late systolic murmur. *G*, Crescendo-decrescendo pulmonary ejection murmur. Abbreviations: *AA*, aortic area, *PA*, pulmonary area; *MA*, mitral area, *LSB*, left sternal border. The distance between heavy vertical lines = 0 2 second.

murmur from an ejection systolic murmur, which, if aortic, may be loudest at the apex. In these instances, however, the differentiation can usually be made by the change in intensity of the murmurs after the patient has inhaled amyl nitrite. Whereas the regurgitant systolic murmur of mitral incompetence fades after the patient has inhaled this drug, ejection systolic murmurs will increase in intensity.[25,26]

"Vibratory" systolic murmur. This innocent murmur was first described by Still[27] in 1909, and since then by numerous other authors.[10,18,23-32] It is extremely common in childhood but also occurs in young adults.[10,30] The murmur is low pitched and musical, and is often audible over the whole precordium, although it is usually loudest just inside the apex. It may radiate into the neck[18] and, therefore, may be difficult to distinguish from an aortic ejection murmur. Like the latter it increases in intensity with exercise[10,29,30,33] and after inhalation of amyl nitrite.[26,29] The vibratory murmur should usually be recognized by its typical low-pitched, musical intonation, but, where difficulty still exists, a phonocardiogram will demonstrate the low-frequency (75 to 160 cycles per second), uniform vibrations of this short crescendo-decrescendo systolic murmur (Fig. 1,*B*).[10,18,29,30,34,35]

The cause of the murmur is unknown and it may, in fact, represent an *innocent* aortic ejection systolic murmur, as postulated by Stuckey.[34] Other theories are that it is caused by vibration of the heart muscle[18] or trigonoidation of the pulmonary cusps,[27] or that it is exocardial.[27]

Atypical systolic murmur of small ventricular septal defect. The typical crescendo-decrescendo pansystolic murmur of a small ventricular septal defect (Fig. 1,*D*) is unlikely to be confused with an aort ejection systolic murmur. The mu

the vascular bruit may then resemble a transmitted systolic murmur. Pressure on the vein, however, will invariably abolish or decrease any murmur of venous origin. Arterial bruits are also often audible in the neck and, like the venous hum, are most common in infants and children. The exact mechanism of production is uncertain, but it has been postulated that they arise in the aortic arch[8] or at the origin of the right carotid artery from the innominate artery.[10] These arterial bruits are typically short but are later in onset (on a phonocardiogram 0.12 to 0.16 second after the beginning of the QRS complex) than ejection systolic murmurs.[8]

Murmurs which arise at the aortic valve and are transmitted to the carotid arteries sound similar both in the neck and over the precordium. This feature is useful in distinguishing them from pulmonary ejection systolic murmurs which may be associated coincidentally with cervical arterial bruits, since in such instances there is a difference in character between the murmur in the neck and that heard over the chest.

Differential diagnosis of an isolated systolic murmur

There are six other systolic murmurs which may be associated with a normal second heart sound, electrocardiogram, and x-ray film. These are: pulmonary ejection systolic murmur, late systolic murmur, regurgitant systolic murmur of mitral incompetence, "vibratory" systolic murmur, atypical systolic murmur of small ventricular septal defect, cardiorespiratory murmur. These six types of murmur and their differentiation from an aortic ejection murmur will now be discussed in some detail.

Pulmonary ejection systolic murmur (*Fig. 1,G*). Pulmonary ejection murmurs are usually loudest in the second left intercostal space but may also be heard over the aortic area, sternal border, and apex. When loud, they may be audible in the neck, especially on the left side,[11] but unlike aortic ejection murmurs—and this we regard as the most important distinguishing feature—they do not radiate specifically up the carotid arteries.

Isolated pulmonary systolic murmurs without abnormality of the pulmonary valve are extremely common[12] and are attributed to "flow," which may be normal or increased, for example, in atrial septal defect, pregnancy, anemia, or thyrotoxicosis.

Organic disease of the valve is usually congenital, but, rarely, it may be due to rheumatic involvement[13] and is then always associated with other valvular lesions. Pulmonary stenosis, even when mild, is characterized by a harsh, loud systolic murmur and a soft, delayed pulmonary component of the second heart sound. An early ejection click is often present. Idiopathic dilatation of the pulmonary artery may also cause a pulmonary ejection systolic murmur and an ejection click, but in this instance the pulmonary component of the second sound is normal or even increased in intensity.

Late systolic murmur. This systolic murmur (Fig. 1,*F*), which is either loudest or only audible in late systole, and which is usually best heard at the apex, has been variously interpreted. Either mild mitral incompetence[15,16] or an innocent murmur,[17,18] possibly of pleuropericardial origin,[19] have been the usual explanations. The murmur is often associated with a mid or late systolic click which may arise either from a fibrosed chorda tendinea[20] or a pleuropericardial tag.[21] The significance of these interesting systolic murmurs is the subject of another communication,[22] and for the purpose of the present discussion it suffices to say that, because of their typical late systolic accentuation, they are unlikely to be confused with aortic ejection systolic murmurs.

Regurgitant systolic murmur of mitral incompetence. Although the pansystolic apical regurgitant murmur,[23] which is usually associated with a third heart sound followed by a short mid-diastolic murmur, is characteristic of significant mitral regurgitation, mild incompetence of the mitral valve may result only in a soft systolic murmur (Grade 1 or 2 in intensity according to Levine's classification[24]) localized to the apex (Fig. 1,*E*). The patient with such a murmur may have a normal electrocardiogram and roentgenogram, and, occasionally, one has difficulty in distinguishing this regurgitant

Table I. Data on 20 patients with aortic systolic murmurs

Case	Sex	Age (yr.)	Maximum intensity	Early diastolic murmur	Other murmurs	Relevant history and remarks	Etiology
1.	F	9	1	Soft, short	Grade 1 MISM Short MDM	Chorea × 3	Rheumatic fever
2.	F	10	1	Soft, short	No	Dilated aorta (x-ray). Ejection click. Familial hypercholesterolemia	Atherosclerosis
3.	M	26	2	Soft, short	No	Nil	Bicuspid aortic valve (?)
4.	M	21	1	Soft, short	No	Subacute bacterial endocarditis	Bicuspid aortic valve (?)
5.	F	28	2	Soft, short	No	Nil	Bicuspid aortic valve (?)
6.	F	8	2	Soft, short	Grade 2 Vib.SM	Rheumatic fever at age 6 yr. Family history of rheumatic fever	Rheumatic fever (?)
7.	M	21	3	Soft, short	No	Nil	Bicuspid aortic valve (?)
8.	M	15	2	Transient	No	Rheumatic fever (?) at age 14 yr. Acute nephritis at age 15 yr.	Rheumatic fever (?) Bicuspid aortic valve (?)
9	F	15	1	No	Grade 1 MISM	Rheumatic fever at age 2 yr.	Rheumatic fever
10.	F	9	1	No	Grade 1 Pulm. SM Grade 1 Late SM	Probable rheumatic fever at age 6 yr. Family history of rheumatic fever	Rheumatic fever
11.	M	7	2	No	Short MDM	Dilated aorta (x-ray)	Rheumatic fever
12.	F	17	1	No	Grade 1 MISM	Nil	Rheumatic fever
13.	F	17	2	No	No	Angina pectoris Familial hypercholesterolemia	Atherosclerosis
14.	F	18	3	No	No	Angina pectoris. Familial hypercholesterolemia	Atherosclerosis
15.	F	7	3	No	No	Subacute bacterial endocarditis and nephritis at age 6 yr.	Bicuspid aortic valve (?) Rheumatic fever (?)
16.	M	17	2	No	No	Subacute bacterial endocarditis (?) at age 16 yr. Acute abdomen at age 17 yr.	Bicuspid aortic valve (?) "Arteritis" ??
17.	M	9	3	No	No	Ejection click. Family history of rheumatic fever	Rheumatic fever (?)
18.	M	12	2	No	No	Systolic murmur since birth. Father had proved aortic stenosis	Bicuspid aortic valve (?)
19.	M	12	3	No	No	Nil	Bicuspid aortic valve (?)
20.	M	20	2	No	No	Nil	Bicuspid aortic valve (?)

MISM: Mitral incompetence systolic murmur. MDM: Mid-diastolic murmur. Vib.SM: Vibratory systolic murmur. Pulm. SM: Pulmonary systolic murmur

loud, often associated with a thrill, and usually best heard in the third and fourth left intercostal spaces. Radiation to the carotid arteries is not a feature. However, some patients with very small defects have a shorter systolic murmur which occupies only two thirds of systole and thus resembles an ejection murmur.[6,38,39] This atypical murmur of very small ventricular septal defect—and in the example shown (Fig. 1,*C*) the left-to-right shunt calculated by dye-dilution techniques was only 8 per cent—is usually maximal at the third or fourth left intercostal space. *Occasionally, it may be loudest at the* pulmonary area,[40] so that the similarity to an ejection murmur is then even more *striking. We agree with Vogelpoel and* associates,[39] however, that this atypical murmur of small ventricular septal defect decreases or disappears after the patient has inhaled amyl nitrite, and in this way it can be distinguished with confidence from an ejection systolic murmur.

Cardiorespiratory murmur. The existence of this murmur as a distinct entity is rather doubtful. It has been described by various authors[10,30,41,42] and is said to be heard best at the apex as a high-pitched short "squeal."[30] The most characteristic feature is the variation with respiration. The murmur is possibly an abnormal breath sound produced by entry of air into the overlying lung during ventricular systole.[12,43] It seems likely that in the past many murmurs which showed some respiratory variation were labeled "cardiorespiratory." Most auscultators nowadays ignore breath sounds when listening to a heart, however, and we think that this term should be dropped.

Material and methods

Aortic ejection systolic murmurs. During a period of 1 year, we have examined 20 normotensive patients under the age of 35 years whom we believe have aortic ejection systolic murmurs. All had a normal second heart sound and electrocardiogram. Roentgenograms were normal, except for a slightly dilated aorta in 2 instances (Cases 2 and 11, Table I). The intensity of the systolic murmurs were never more than Grade 3.

Thirteen of the 20 patients were referred to this Cardiac Clinic for assessment of a systolic murmur, whereas the other 7 were found on routine examination of hospital patients. In 15 (Cases 2-5, 7,8,11,13-20) the murmur was audible at the apex, left sternal border, and base. In 4 (Cases 1,9, 10,12) there was an associated regurgitant systolic murmur at the apex which obscured a possible aortic murmur at this site. In 1 patient (Case 6) the aortic murmur was obscured at the apex and left sternal border by an associated vibratory systolic murmur. The murmur was equally loud at the apex and base in 10 patients (Cases 2,4,5,7,8,11,15,16,19,20) *and louder* at the base in 5 (Cases 3,13,14,17,18). In only 1 patient (Case 18) was the murmur *louder at the pulmonary than at the aortic* area. Phonocardiograms were recorded in 17 patients (Cases 1-3, 5-7, 9-17, 19,20), and an early, short crescendo-decrescendo murmur was shown (Fig. 1,*A*). In all the patients the murmur radiated into the neck, and was heard better over the carotid artery than over the adjacent tissues of the neck. It was usually louder over the right than over the left carotid artery.

Systolic murmurs in normal persons. In order to determine the incidence and, therefore, significance of these aortic systolic murmurs, we auscultated 400 normal subjects who were under 35 years of age. These comprised 200 school children, 100 pregnant women, and 100 young adults. All were examined in the supine, left lateral, and sitting positions. Observations on the site, intensity, character, radiation, and probable origin of the systolic murmurs were made, and particular attention was paid to the character of the second heart sound. The presence of cervical bruits, both venous and arterial was also recorded.

Results

1. Analysis of 20 patients with aortic systolic murmurs (Table I). Almost certain proof of the organic nature of the murmur was provided in 8 patients (Cases 1-8) by the presence of an associated soft aortic diastolic murmur. In 1 of these patients (Case 8) the early diastolic murmur was audible only during the hypertensive phase of acute glomerulonephritis.

Circumstantial evidence of aortic valvu-

cent of the subjects had probable pulmonary ejection systolic murmurs. In 9 per cent, we had difficulty in distinguishing between the two murmurs, and in these it seemed likely that both were present.

Cervical systolic bruits, both venous and arterial, were common and were present in over half of the children. In some cases of venous bruits a typical venous hum (i.e., audible in systole and diastole) became audible when the child was in the erect position.

B. ONE HUNDRED PREGNANT WOMEN, AGED 17 TO 33 YEARS (TABLE III). Among the 100 pregnant women (between 16 and 39 weeks pregnant), 81 per cent had systolic murmurs, of which 55 per cent were pulmonary ejection and 11 per cent were vibratory, and in 14 per cent both pulmonary ejection and vibratory systolic murmurs were probably present. Two women, one of whom had an associated vibratory systolic murmur, had continuous murmurs compatible with the so-called mammary souffle.[43] Vascular murmurs in the neck, the majority of which were venous, were present in about a third of the women.

C. ONE HUNDRED YOUNG ADULTS, AGED 17 TO 28 YEARS (TABLE IV). Pulmonary ejection systolic murmurs were found in 53 per cent, vibratory in 3 per cent, and both types were present in 7 per cent. Cervical bruits were heard in about 30 per cent, but only 6 of these were venous in origin. One aortic ejection systolic murmur was found in a 20-year-old man in this group. The murmur was Grade 2 in intensity, audible over the whole precordium, and radiated specifically into the carotid arteries. The second heart sound was normal. There was no history of rheumatic fever or associated evidence of heart disease, and it seems likely that the murmur was caused by a congenital bicuspid aortic valve.

Discussion

It is probable that in our 20 patients with aortic ejection systolic murmurs the underlying pathology was rheumatic fever in 8 (Cases 1,6,8-12,17), congenital bicuspid aortic valve in 9 (Cases 3-5,7, 15,16,18-20), and xanthomatous deposits in 3 (Cases 2,13,14). Thus, there is a relatively high incidence of suspected bicuspid aortic valves in the series. Soulié and associates[44] found this abnormality at autopsy in 0.14 per cent of the general population, whereas Koletsky,[45] who considers it the most common congenital malformation of the heart, reported a 1 per cent incidence. Bacon and Matthews[46] consider that the diagnosis of a bicuspid aortic valve is impossible during life. It is generally agreed, however, that it should be suspected by the appearance of subacute bacterial endocarditis in an individual whose heart had previously been regarded to be normal.[47-50] Three of our patients (Cases 4,15,16) are thought to have had subacute bacterial endocarditis, and we believe that all had bicuspid valves. Bentivoglio and associates[51] maintain that a bicuspid aortic valve, even when uncomplicated, will cause a systolic murmur because it is unable to open completely. Edwards[52] agrees that an anatomically perfect bicuspid valve cannot open fully, but postulates that excessive length of one or both cusps prevents stenosis. It would seem likely that such a valve, even if not stenotic, could produce a soft systolic murmur, and at the present time it remains uncertain whether a bicuspid valve can ever be completely silent. In any event, bicuspid valves are particularly subject to trauma, with the consequent early development of degenerative sclerosis,[46,52] so that a systolic murmur from this cause could be expected at an early stage.

The patients with familial hypercholesterolemia in our series (Cases 2,13,14) are thought to have atheromatous deposits on the aortic valve which produce an aortic ejection systolic murmur. The normal aging process is hastened in patients who have xanthomatosis, with pathologic changes similar to those found in cases of atheroma,[16] and patients who have familial hypercholesterolemic xanthomatosis may show anatomic evidence of extensive valvular involvement at an early age.[53]

Other rarer causes of minimal aortic valvular disease include Hunter's polydystrophy,[54,55] rheumatoid arthritis,[56] and ankylosing spondylitis.[57,58] Aortic ejection murmurs which are not due to disease of the valve have been described in associa-

Table II. Incidence of systolic murmurs in 200 normal children, aged 2 to 12 years

Sex		*Percentage with systolic murmurs*			
M	*F*	*Vibratory*	*Pulmonary ejection*	*Both*	*Total*
53	47	58	17	9	84

Table III. Incidence of systolic murmurs in 100 normal pregnant women, aged 17 to 33 years

Number of women	*Percentage with systolic murmurs*				
	Vibratory	*Pulmonary ejection*	*Both*	*Mammary souffle*	*Total*
100	11*	55	14	1	81

*One patient had a mammary souffle

Table IV. Incidence of systolic murmurs in 100 normal young adults, aged 17 to 28 years

Sex		*Percentage with systolic murmurs*				
M	*F*	*Vibratory*	*Pulmonary ejection*	*Both*	*Aortic*	*Total*
50	50	3	53	7	1	64

lar disease was present in 10 of the other 12 patients. Four patients (Cases 9-12), 2 of whom had a past history of rheumatic fever (Cases 9 and 10), had mild mitral valvular disease with soft mitral systolic or diastolic murmurs. The aortic systolic murmur in these 4 patients was probably due to involvement of the aortic valve by the rheumatic process. Two patients with familial hypercholesterolemic xanthomatosis (Cases 13 and 14) were thought to have atheromatous deposits on the aortic valve. Two patients (Cases 15 and 16) presented with subacute bacterial endocarditis. One patient (Case 17) with a family history of rheumatic fever had an aortic ejection click. Another patient (Case 18), whose father had been operated on for calcific aortic stenosis, was known to have had a systolic murmur since birth. Only 2 patients (Cases 19 and 20) had no history or other signs suggestive of heart disease, and they had aortic systolic murmurs which were identical to the others in the series.

2. Analysis of 400 normal control subjects. Despite a high incidence of systolic murmurs in the 400 normal control subjects, in only one instance did we find a murmur identical to those found in the 20 patients in whom we think minimal aortic valvular disease is present.

A. TWO HUNDRED CHILDREN, AGED 2 TO 12 YEARS (TABLE II). In common with previous series,[28-30] we found a high incidence (58 per cent) of "vibratory" systolic murmurs among the 200 children examined. When the murmur was Grade 2-3 in intensity, it was usually heard well over the carotid arteries, and this appeared to be a specific radiation, similar to that heard in aortic ejection systolic murmurs. Seventeen per

We are very grateful to Dr. S. Johnson, of the City Health Department, and Dr. V. Mitchell, of the School Clinic, Johannesburg, for allowing us to auscultate the normal children; also to Dr. J. Samson, of the Queen Victoria Maternity Hospital, who gave us permission to auscultate the pregnant women. We wish to thank Professor G. A. Elliott for his encouragement in the preparation of this paper, and Dr. K. F. Mills, Superintendent of the Johannesburg General Hospital, for permission to publish.

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tion with dilatation of the aorta,[33,59] obstruction of the left ventricular outflow tract,[60,61] and a narrowed anteroposterior diameter of the chest, as seen in depressed sternum[62] or "straight back" syndrome.[63]

The aortic ejection systolic murmur which is commonly present in patients with hypertension is probably often a hemodynamic effect since the valve may be anatomically normal.[2] The murmur may sometimes be caused by dilatation of the aorta[33] or, in the elderly hypertensive person, by minimal sclerosis of the valve.[1]

Aortic systolic murmurs due to increased flow across a normal valve are recognized by some authors,[62,64] but, in our experience, do not occur in high-output states, such as anemia and thyrotoxicosis, in which cases we believe that the systolic murmur present is invariably pulmonary ejection. The assessment of systolic murmurs may be difficult in pregnant women since the pulmonary ejection systolic murmurs are harsher than usual; and possibly because of displacement of the heart, they are often well heard at the aortic area. In addition, a high incidence of cervical bruits may make differentiation from aortic murmurs difficult. Thus, it would seem necessary sometimes to delay the final assessment of a systolic murmur in pregnancy until a few weeks after delivery.

Conclusions

The evidence presented in this paper suggests that, in normotensive subjects, an aortic systolic murmur, even of Grade 1 intensity, indicates minimal valvular disease or aortic dilatation. Two probable exceptions to this are the vibratory murmur of childhood and the aortic ejection murmur found in some hypertensive patients. The mode of production of these two murmurs is as yet not fully understood.

The importance of recognizing the site of origin of these systolic murmurs lies in their etiology, since they are usually due to rheumatic involvement or to a congenital bicuspid valve. Prophylaxis of rheumatic fever is necessary in the former instance, and precautions against subacute bacterial endocarditis are indicated in both. Bicuspid valves are particularly liable to develop subacute bacterial endocarditis,[47,48,52,65] and an incidence as high as 25 per cent has been given.[62] In many patients with bacterial endocarditis the heart had previously been considered to be normal, and a systolic murmur to be "innocent" or of no significance.[50] Furthermore, some patients with full-blown calcific aortic stenosis are reported to have had "innocent" basal systolic murmurs 10 to 20 years previously.[42,62,66,67] We agree with Bacon and Matthews[46] that many of these may be due to bicuspid valves, which are known to be particularly subject to trauma, with the early development of degenerative sclerosis[46,52] and, consequently, stenosis. Therefore, this future complication should be borne in mind in patients, particularly males, in whom a clinical diagnosis of a bicuspid aortic valve is made.

Summary

The clinical features of an isolated aortic ejection systolic murmur are described, and the differentiation from other systolic murmurs is discussed.

It is postulated that, in the absence of hypertension, such an aortic ejection systolic murmur is seldom or never "functional" and invariably implies that a congenital bicuspid valve, minimal disease of the valve, or a dilated aorta is present.

Evidence is produced which suggests that 20 normotensive patients, under the age of 35 years, with aortic ejection systolic murmurs have abnormal aortic valves.

Four hundred normal subjects, including 200 children, 100 young adults, and 100 pregnant women, were auscultated in order to assess the incidence of an isolated aortic systolic murmur; such a murmur was present in only one instance. This was in a 20-year-old man, and it seems likely that he has a congenital bicuspid aortic valve.

The recognition of an abnormal, even though not stenotic, aortic valve in young people is important, particularly in relation to the prophylaxis of rheumatic fever and subacute bacterial endocarditis. The possible development in later life of calcific aortic stenosis in some subjects, particularly males, with bicuspid valves should be borne in mind.

Pulmonary diffusing capacity and pulmonary capillary blood volume in normal subjects and in cardiac patients

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Many reports have appeared in the literature assessing the pulmonary diffusing capacity for carbon monoxide in patients with mitral valvular and other cardiac lesions.[1-10] In general, the diffusing capacity was either normal or reduced in patients with mitral valvular disease, and it was elevated in patients with intracardiac shunts.

By means of the carbon-monoxide breath-holding technique described by Forster, Roughton and associates,[11-13] and other modified methods,[7,14,15] it has been feasible to measure the pulmonary capillary volume and to study the behavior of the pulmonary capillary bed in man. Values of the pulmonary capillary volume have been reported in normal subjects and in patients with various types of cardiopulmonary lesions at rest, during change of position, and during exercise.[6,7,9,16]

The purpose of this paper is to report the pulmonary diffusing capacity for carbon monoxide (D_{LCO}) and pulmonary capillary blood volume (V_C) in a group of normal subjects and in many cardiac patients, and to correlate the pulmonary capillary blood volume and pulmonary blood flow and pressures in the cardiac patients.

Material and methods

Normal subjects were selected from hospital and laboratory personnel who had no evidence of cardiopulmonary disease. The diagnoses of the cardiac lesions in patients were made on the basis of clinical, hemodynamic, and, in many instances, operative findings.

The studies were carried out in two parts: (1) D_{LCO} was determined in 27 normal subjects and in 59 patients (divided into 5 groups) with various cardiac lesions. Two to 16 determinations of D_{LCO} were performed on each individual. The average values for each normal subject or patient were used to obtain the mean for each

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Table I. Multiple determinations of pulmonary diffusing capacity for carbon monoxide and pulmonary capillary blood volume in a series of normal subjects

Subjects	$D_{L_{CO}}$ (ml./mm. Hg/min.)			V_C (ml./M.² BSA)		
	A	B	C	A	B	C
H.C.	21.6*	21.1	19.7			
	20.8	20.8	18.9	31.6*	31.3	20.5
				33.7	33.4	21.4
	20.2	20.8	20.6			
	20.2	19.4	18.5			
P.P.	29.6	32.2	34.5			
	33.4	31.8	34.7			
				42.4	39.0	
				47.5		
	28.2					
	28.9					
J.F.	28.8	32.2	31.4			
	30.3	32.4	29.7	33.1	31.2	37.6
D.S.	39.5	41.6				
	37.8	39.7				
				43.6	47.0	
				42.6	42.6	
	35.6	39.5				
	39.5	40.1				
J.P.	25.5	25.5				
	25.3	28.4				
				60.5	50.0	
				60.0		
	24.1					
	24.7					
M.L.	28.6					
	29.1					
				41.5		
				40.4		
	28.0					
	30.2					
F.L.	20.3					
	19.3					
				25.7		
				27.6		
	24.4					
	20.5					
P.Y.	30.8	30.2				
	31.5	26.8				
				32.0	43.0	
				34.3		
	31.4					
	28.6					
W.J.	30.3					
	30.1					
				43.7		
				43.5		
	27.6					
	28.9					

*The paired figures of either $D_{L_{CO}}$ or V_C denote the results of duplicate determinations.
$D_{L_{CO}}$: Pulmonary diffusing capacity for carbon monoxide. V_C: Pulmonary capillary blood volume. A, B, and C: Different dates on which the determinations of $D_{L_{CO}}$ and V_C were made.

group. (2) V_C was measured in 13 normal subjects and in 44 patients with cardiac lesions. Information in regard to pulmonary blood flow and vascular pressures was also obtained in the latter group.

In all the normal subjects and in all but 5 patients with interatrial septal defects, estimate of the V_C was made with the subject in a recumbent position. The V_C in these 5 patients was determined with the subject in a standing position.

D_{LCO} was determined by the breath-holding method of Forster and associates.[1] The apparatus consisted of a Donald-Christie bag-box system* connected to a 9-liter spirometer by unidirectional flow valves and a three-way manual valve. A 6-liter sampling bag was interposed in the circuit near the mouthpiece. The sampling bag was evacuated and closed. The reservoir bag was filled with a mixture of 0.3 per cent carbon monoxide (CO) and 10 per cent helium (He) in air. The patient's residual volume was previously measured by the helium-dilution technique.[17] To perform the study, the patient was asked to exhale completely to his residual volume. He then took a rapid maximum inspiration of the CO mixture from the reservoir bag through a line flushed with the bag mixture. The inspiration was held for approximately 9 to 10 seconds, after which he exhaled completely. After elimination of about 750 ml. of gas, a sample of the expired "alveolar" gas was obtained in the sampling bag near the mouthpiece.

For the estimation of V_C, D_{LCO} was determined at ambient oxygen tension (room air) as well as at high levels of oxygen (O_2). This was accomplished by using two mixtures of 0.3 per cent CO and 10 per cent He, one in room air and the other in O_2; both mixtures were held in Donald-Christie bag-box systems. Prior to the determination of D_{LCO} at high O_2 level, the patient was asked to breathe 100 per cent O_2 for 2 to 3 minutes. Repeated determination of D_{LCO} resulted in a rise in carboxyhemoglobin and CO back pressure. To correct for this effect in the calculation of serial D_{LCO}, the initial and final carboxyhemoglobin levels were calculated according to the method described by Forster and Roughton. These were done (a) by having the patients wash out the nitrogen in the lungs and rebreathe for 5 minutes in a 5-liter bag which contained 100 per cent O_2 through a CO_2 absorbent, and (b) by measuring the oxygen tensions and CO concentrations in the bag which were assumed to be equilibrated with capillary blood. The carboxyhemoglobin levels were estimated in this way at the beginning and the end of each study. The CO back pressure was then calculated from the carboxyhemoglobin levels, at each determination of D_{LCO}, approximated by interpolation from the initial and final values.

According to the method of Forster and Roughton,[11,12] the reciprocals of diffusing capacities calculated from the modified Krogh formula were plotted against the reciprocals of θ, reaction rate of CO with hemoglobin, using a λ value of 2.5. From the data, V_C was then estimated graphically.

The concentrations of CO, He, and O_2 in the initial gas from the reservoir bag and the expired "alveolar" gas from the sample bag were dried and passed through a CO_2 absorbent and measured by an infrared CO analyzer,* a Katharameter for analysis of He,† and a paramagnetic O_2 analyzer,‡ connected in a series.

The inspired volume and the duration of breath-holding were measured from the spirometer tracing. The end point of breath-holding was taken at the beginning of "alveolar" sampling.

D_{LCO} is expressed in milliliters per millimeter of mercury per minute (ml./mm. Hg/min.), and V_C in milliliters per square meter of body surface area (ml./M.^{2}BSA). Hereinafter, the values of D_{LCO} referred to in the text and tables were obtained at ambient oxygen tension. In all except the 5 patients with interatrial septal defects, V_C was measured in conjunction with right heart catheterization. To confirm or rule out any intracardiac lesions, samples of blood from the heart chambers were obtained for gas analysis by the Van Slyke

*Warren E. Collins, Inc., Boston, Mass.

*Liston-Becker Model 15A (Beckman), sensitive to a change of 15 p.p.m. of CO set up in our laboratory.

†Gow-Mac. Appropriate corrections were made for the effect of varying oxygen tensions on the thermal conductivity of the helium analyzer.

‡Beckman Model C.

cardiac patients

Height (cm.)		Weight (Kg.)		BSA (M.²)		D_{LCO} (room air)	
Range	Mean	Range	Mean	Range	Mean	Range	Mean
150–190	170	49.0–86.4	70.6	1.40–2.16	1.82	16.3–45.5	29.3
150–190	167	49.0–86.4	70.7	1.40–2.16	1.81	20.1–45.5	29.6
157–183	172	60.4–79.5	70.1	1.60–2.00	1.84	16.3–41.8	28.7
155–190	174	60.4–86.4	74.2	1.70–2.16	1.90	16.3–45.5	31.6
150–168	161	49.0–85.5	62.9	1.40–1.95	1.66	18.0–30.0	24.9
165–183	174	63.1–79.0	69.5	1.70–1.94	1.83	20.3–39.3	30.9
157–190	173	54.6–84.0	71.4	1.56–2.15	1.85	23.0–35.3	26.3
157–179	177	51.4–71.4	63.1	1.50–1.86	1.70	18.3–38.2	25.6
155–182	168	47.3–85.0	68.2	1.56–2.02	1.78	13.5–38.2	22.0
152–175	163	42.2–76.4	59.8	1.34–1.90	1.64	21.4–52.5*	30.9

insufficiency. MS: Mitral stenosis. IASD Interatrial septal defect.

between the mean D_{LCO} in normal subjects and that in patients with aortic valvular lesions, mitral insufficiency, and Class II mitral stenosis. In 2 patients with interatrial septal defects, D_{LCO} was greater than the upper limit of normal subjects, but the mean D_{LCO} in this group showed no difference from that of the normal subjects. In contrast with the finding in normal subjects, the mean D_{LCO} in patients with Class III or Class IV mitral stenosis was significantly decreased ($p < 0.01$). In most patients of this group there was clinical and radiologic evidence of pulmonary congestion or edema. However, as shown in Fig. 1, there was no significant coefficient of correlation between the pulmonary diffusing capacity and (a) pulmonary arterial mean pressure or (b) pulmonary wedge mean pressure.

C. Pulmonary capillary blood volume (V_C). The values of V_C in 13 normal subjects and in 44 patients at rest are presented in Table III. In these patients, data on pulmonary blood flow and pulmonary arterial and pulmonary wedge pressures are also included.

The mean V_C was within normal limits in patients with aortic valvular lesions and in those with mitral insufficiency. There was a significant increase in mean V_C in patients with Class II mitral stenosis,

Table III. Pulmonary capillary blood volume, pulmonary blood flow, and pulmonary arterial and wedge pressures in normal subjects and in cardiac patients

Diagnosis	Number of cases	V_C		Q_P		PA_m		PC_m	
		Range	Mean	Range	Mean	Range	Mean	Range	Mean
Normal subjects	13	26.7–71.8	43.0						
AS and/or AI	7	37.6–77.8	47.3	2.35–4.88	3.48	15–24	18	8–19	12
MI	7	21.7–73.0	47.6	1.84–4.62	3.25	12–56	32	7–28	18
MS (Class II)	10	40.6–73.5	57.4	2.04–3.76	2.78	16–48	26	8–25	16
MS (Class III or IV)	10	33.0–105.0	72.0	1.18–4.24	2.73	18–65	43	11–30	23
IASD	10	53.0–162.0*	88.3	6.71–14.85	9.61	9–22	15	4–12	8

*In 5 cases the V_C was determined while the patient was in the standing position.
The abbreviations for the diagnoses are identical to those used in Table II.
V_C: Pulmonary capillary blood volume (mL/M² BSA). Q_P: Pulmonary blood flow (L./M²/min.). PA_m: Pulmonary arterial mean pressure (mm.Hg). PC_m: Pulmonary wedge mean pressure (mm Hg).

Table II. Physical characteristics and pulmonary diffusing capacity of normal subjects and

Group	Diagnosis	Number of cases	Age (yr.)		Sex	
			Range	Mean	Male	Female
1.	Normal subjects (whole group)	27	14–70	33	18	9
	Below the age of 35	19	14–34	25	11	8
	Above the age of 35	8	35–70	56	7	1
	Male	18	14–70	37	18	
	Female	9	19–57	26		9
2.	AS and/or AI	7	15–46	27	7	0
3	MI	7	21–49	32	5	2
4.	MS (Class II)	12	23–43	33	4	8
5.	MS (Class III or IV)	16	25–62	39	8	8
6.	IASD	17	14–49	25	7	10

*In 5 cases the D_{LCO} was determined while the patient was in the standing position
D_{LCO} Pulmonary diffusing capacity for carbon monoxide (ml./mm.Hg/min.). AS Aortic stenosis AI: Aortic insufficiency. MI. Mitral

manometric method, and indicator-dilution curves were inscribed according to the method described elsewhere.[18] Systemic arterial (BA), pulmonary arterial (PA), and pulmonary wedge (PC) pressures were measured by means of strain-gauge transducers and recorded on a multichannel Sanborn recorder. The upper limits of normal mean PA and PC pressures in our laboratory are 20 and 12 mm. Hg, respectively. With the cardiac catheter in the pulmonary artery for sampling mixed venous blood, pulmonary blood flow (Q_P) was estimated by the Fick procedure, on the assumption that the pulmonary venous blood was 98 per cent saturated. In our laboratory the pulmonary blood flow in normal subjects varied between 2.8 and 5.0 L./M.²BSA. In patients without intracardiac shunts, pulmonary and systemic blood flows are considered to be equal. In patients with intracardiac shunts, approximate systemic blood flow was determined by using the oxygen difference between the sample of blood obtained from a systemic artery and that obtained from the superior vena cava.

After pulmonary blood flow had been determined and intravascular pressures recorded, the patients were connected to the Donald-Christie bag-box system described above, and the diffusing procedure at ambient oxygen tension and high levels of oxygen was performed. Two to 4 determinations were made at each level. BA, PA, and PC pressures were again checked at the end of the procedure.

Results

A. Reproducibility of the values. In order to ascertain the reproducibility and range of normal variations of D_{LCO} and V_C which were measured in our laboratory, statistical analysis was made on duplicate determinations of D_{LCO} in 27 normal subjects and in 32 cardiac patients, and of V_C in 13 normal subjects. The standard deviation of the difference between duplicate determinations of D_{LCO} in normal subjects was found to be 1.705; that of D_{LCO} in cardiac patients was 1.40, and that of V_C was 3.956. In other words, the values between duplicate determinations of D_{LCO} would rarely (< 5 per cent) differ by more than 4.8 ml./mm. Hg/min., and those of V_C by more than 11 ml./M.²BSA.

Some of the data on D_{LCO} and V_C obtained from 9 normal subjects by repeated determinations on a single day or on different days are presented in Table I.

B. Pulmonary diffusing capacity (D_{LCO}). The values for D_{LCO} in 27 normal subjects and in 59 patients with various cardiac lesions are listed in Table II. Among the normal subjects no difference in the mean D_{LCO} was observed between those who were below the age of 35 and those who were above the age of 35. The mean D_{LCO} in 9 females was lower than that in 18 males. There was no statistical difference

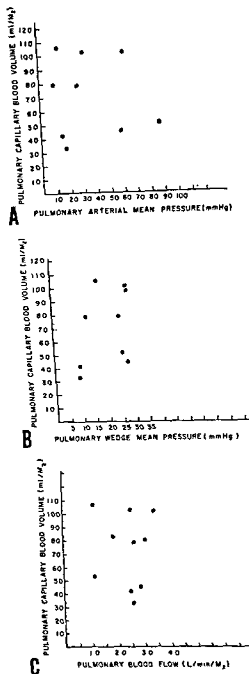


Fig. 2. Relationship of pulmonary capillary blood volume to (*A*) pulmonary arterial mean pressure, (*B*) pulmonary wedge mean pressure, and (*C*) pulmonary blood volume in patients with Class III or Class IV mitral stenosis. There was no significant correlation between any two of these parameters (r = 0.009, 0.465, and 0.152, respectively).

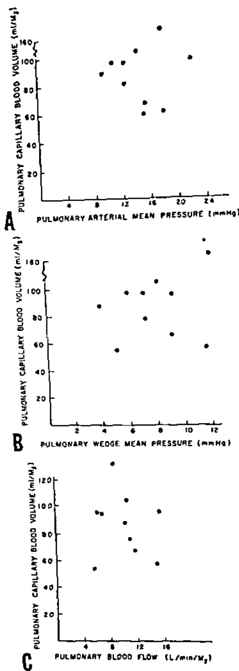


Fig. 3. Relationship of pulmonary blood volume to (*A*) pulmonary arterial mean pressure, (*B*) pulmonary wedge mean pressure, and (*C*) pulmonary blood flow in patients with interatrial septal defects. There was no significant correlation between any two of these parameters (r = 0.106, 0.341, and −0.219, respectively).

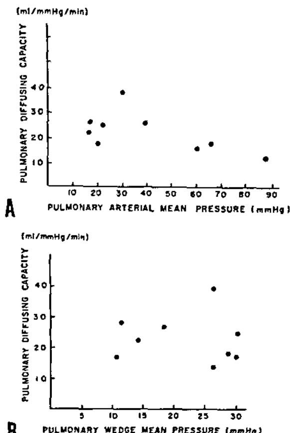


Fig. *1.* Relationship of pulmonary diffusing capacity to (*A*) pulmonary arterial mean pressure and (*B*) pulmonary wedge mean pressure in patients with Class III or Class IV *mitral stenosis. No significant* correlation was observed in either case (r = −0.57 and −0.07, respectively).

as compared with that in normal subjects. A highly significant increase in mean V_C was observed in patients with Class III or Class IV mitral stenosis and in those with interatrial septal defects. In 8 of the 10 patients with interatrial septal defects the V_C was greater than the upper range *of the normal subjects.*

Although pulmonary blood flow in patients with interatrial septal defects was markedly increased, its mean value was within normal limits in the other groups of patients. The PA_m and PC_m pressures were normal in patients with aortic valvular lesions and *in those with interatrial* septal defects. In contrast, both PA_m and PC_m *pressures were significantly increased* in patients with mitral valvular lesions; the values were greatest in those with Class III or Class IV mitral stenosis.

Figs. 2 and 3 show graphically the pulmonary capillary blood volume in patients with Class III or Class IV mitral stenosis and in those with interatrial septal defects, plotted against the respective individual (a) pulmonary blood flow, (b) pulmonary arterial mean pressure, or (c) pulmonary wedge mean pressure. No significant coefficient of correlation was found between any two parameters.

Discussion

The method used in the present study for measurement of D_{LCO} and V_C was essentially the same as that described by Forster, Roughton and associates.[1,13] Several general assumptions were made: (a) the ratio of diffusing capacity to alveolar volume was considered to be uniform throughout all alveoli; (b) both V_C and D_M were stable and independent of change in the alveolar oxygen tension, and (c) a *λ value of 2.5 was assumed and used for* the computation of θ. The values of θ determined in vitro at this value of λ were considered to be correct.[11,12] These assumptions and limitations have been discussed by Forster, Lewis and their respective associates.[1,12,13,16]

In addition, it is important to point out other potential limitations and possible errors in the technique and calculations employed in our laboratory. First, the *values of V_C have been adjusted from the* oxygen capacity determined in the sample of peripheral blood to a standard capacity of 20 volumes per cent. However, the hematocrit in the pulmonary capillaries may be less than that in the systemic blood. If this is true, our values of V_C would be artificially low. Secondly, to determine the mean pulmonary capillary blood oxygen tension when the alveolar oxygen tension was less than 200 mm. Hg, an arbitrary figure of 5 mm. Hg was subtracted from the measured alveolar oxygen tension. Thirdly, corrections were made in the calculations of V_C for increasing carboxyhemoglobin levels with serial de*terminations of D_{LCO}. The level of car*boxyhemoglobin at each determination of D_{LCO} was estimated by interpolation from values obtained at the beginning and end of each series. However, it has been shown recently by Cadigan and co-workers[16]

In conditions in which there is a great increase in pulmonary blood flow (interatrial septal defect) the mean V_C was approximately twice the mean normal value, and the increase was highly significant ($p < 0.001$). It should be pointed out that in 5 of these patients the V_C was determined while the patient was in the standing position, and that the values so obtained were generally lower than those determined when the patient was in the recumbent position. Therefore, if the determination of V_C in these 5 patients was made when they were in the recumbent position, the mean V_C would be even greater. The findings of increased V_C in patients who have an interatrial septal defect are in agreement with those reported by other workers.[3,4,9]

A significant increase in D_{LCO} in patients with interatrial septal defects was demonstrated by some investigators.[5,9] We were unable to explain why in our patients as a group the D_{LCO} did not increase proportionately with the V_C. Some workers have shown that increased pulmonary blood flow may not necessarily be associated with any increase in pulmonary diffusion capacity.[20,21]

From our data it appears that the pulmonary vascular bed in patients with cardiac lesions may be influenced or governed principally by both pulmonary wedge (or pulmonary venous) pressure and pulmonary blood flow. An increase in pulmonary capillary volume may occur in conditions in which (a) there is an elevation of the pulmonary wedge pressure but no concomitant increase in pulmonary blood flow, and (b) there is a great increase in pulmonary blood flow but normal pulmonary wedge pressure.

Summary

1. Pulmonary diffusing capacity for carbon monoxide (D_{LCO}) was determined in 27 normal subjects and in 59 patients with cardiac lesions. The respective mean values of D_{LCO} (milliliters per millimeter of mercury per minute) were as follows: (a) in normal subjects, 29.3; (b) in patients with aortic valvular lesions, 30.9; (c) in patients with mitral insufficiency, 26 3; (d) in patients with Class II mitral stenosis, 25.6; (e) in patients with Class III and Class IV mitral stenosis, 22.0; and (f) in patients with interatrial septal defect, 30.9. In general, D_{LCO} was within normal limits in patients with mild or moderately severe cardiac lesions, irrespective of the magnitude of pulmonary blood flow, and it was significantly reduced in those with severe mitral stenosis and pulmonary congestion or edema.

2. Pulmonary capillary blood volume (V_C) was estimated in 13 normal subjects and in 44 cardiac patients. The respective mean values of V_C (milliliters per square meter of body surface area) were as follows: (a) in normal subjects, 43.0; (b) in patients with aortic valvular lesions, 47.3; (c) in patients with mitral insufficiency, 47.6; (d) in patients with Class II mitral stenosis, 57.4; (e) in patients with Class III or Class IV mitral stenosis, 72.0; (f) in patients with interatrial septal defect, 88.3.

3. There was an increase in V_C in patients with mitral stenosis who had markedly elevated pulmonary wedge pressure but normal or reduced pulmonary blood flow. A significant increase in V_C was also demonstrated in patients with interatrial septal defect who had an increased pulmonary blood flow but normal pulmonary wedge pressure. It appears that both pulmonary blood flow and pulmonary wedge pressure are important factors which govern the pulmonary capillary bed.

We wish to express our thanks and appreciation to Dr. Robert E. Forster, Professor of Physiology, The Graduate School of Medicine, University of Pennsylvania, for his advice and suggestions in preparing this manuscript. We are indebted to Dr. Arthur Dutton, Associate Professor of Radiation Biology and Scientist (Statistics), Atomic Energy Project, University of Rochester, for his help on the statistical aspects of this study. We are grateful to Mr. Waddell Johnson for his technical assistance and to Mrs. Paula Robbins and Mrs. Bonnie Sollie for their secretarial assistance.

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that the effective carbon monoxide back pressure did not measurably alter duplicate single-breath determinations.

Values of D_{LCO} were obtained only at *ambient oxygen tension (with the subject* breathing room air) and at high oxygen tension (with the subject breathing 100 per cent oxygen). It was our experience, as well as that of other investigators,[19] that, when the subjects were breathing either room air or 100 per cent oxygen, a more accurate estimate of actual alveolar oxygen tension was possible than when intermediate levels of oxygen tension were used, because under the latter circumstances the distribution of inspired gas becomes a large factor in determining the final oxygen tension.

Cadigan and co-workers[10] have demonstrated that in the single-breath method *the variations between multiple tests* were due mainly to variations in the volumes of the lungs (V_A) at which the breath was held. When V_A was controlled at 95 to 100 per cent of the total lung capacity, the coefficient of variation was reduced to a minimum. Although in the present study *the V_A was not controlled, each subject* was instructed to take a maximum inspiratory volume prior to the breath-holding. Thus, in practice, the V_A probably reached 90 to 100 per cent of the total lung capacity in each case. The achievement of maximum V_A may explain the *consistency and reproducibility* of both D_{LCO} and V_C in the subjects included in the present study.

The values of both D_{LCO} and V_C in our series of normal subjects agreed very closely with those reported by other workers using the same method.[2,3,10,16] In patients with aortic valvular disease the mean values of D_{LCO}, V_C, Q_P, PC_m and PA_m were all within normal limits. However, a decrease in D_{LCO} and an increase in V_C were observed in several patients. Thus, *in most of these patients neither* the alveolar-capillary membrane nor the pulmonary vascular bed was as yet significantly altered. It would be reasonable to assume that if this group of patients showed left ventricular decompensation and pulmonary congestion, D_{LCO} might be expected to be reduced and V_C to be increased.

We are unable to explain why the mean V_C was not increased in patients with predominantly mitral insufficiency. Since both PC_m and PA_m were elevated, some *degree of pulmonary congestion might* have been expected in a certain number of patients. One or both of the following factors may be responsible: (a) the mean PC pressure may be influenced by the cyclic high V wave transmitted during ventricular systole, and (b) the large reservoir of the left atrium-pulmonary vein in these patients may not affect the *V_C as acutely or significantly as it does in* those with severe mitral stenosis. Bates and associates,[7] using a steady-state method, found that V_C did not increase even during exercise in some of their patients with mild mitral valvular lesions.

On the other hand, D_{LCO} was decreased *and V_C was increased in patients with* severe mitral stenosis. The decrease in D_{LCO} is not explainable on the basis of sex distribution alone (see Table II). In this group of patients, both pulmonary arterial and pulmonary wedge pressures were markedly elevated, although the *mean pulmonary blood flow was only* slightly reduced. It is very likely that in these patients there was an appreciable degree of congestion of the pulmonary vascular bed, on the one hand, and thickened pulmonary capillary membrane with possible fibrosis, on the other. These find*ings were in conformity with those re*ported by other workers.[1,3,7]

It has been assumed that many of the respiratory symptoms and signs in congestive failure are secondary to pulmonary vascular congestion which involves pulmonary veins and pulmonary capillaries. This eventually may progress to pulmonary edema. Our study would seem to demonstrate that, in general, there is a correlation between symptoms and V_C in many patients with mitral stenosis. *However, in some patients with symptoms* and an elevated mean PC pressure, the V_C was not appreciably altered. This would seem to imply that in these cases without demonstrable changes in V_C an *increased blood volume in the pulmonary* arteries and/or veins may be one of the factors responsible for the production of respiratory symptoms.

Variations in the response of the systolic murmur to vasoactive drugs in ventricular septal defect, with special reference to the paradoxical response in large defects with pulmonary hypertension

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There is a conspicuous variation in the response of the murmurs of ventricular septal defect to the vasoactive drugs, amyl nitrite and phenylephrine. Like all other parameters, this is related to the size of the defect and the resultant hemodynamic adjustments. In previous communications, we stressed the softening of the systolic murmur after amyl nitrite[1] and the intensification after phenylephrine[2] which occurred in small or moderate-sized defects without pulmonary hypertension. When the defects were large or associated with pulmonary stenosis, less consistent changes in the murmur were observed.[1]

We now draw attention to two other types of response which can occur. In the first, the murmur intensifies instead of softening after amyl nitrite, and softens instead of intensifying after phenylephrine. Because this behavior was unexpected and misleading when first observed, it has been termed "paradoxical." However, it is the characteristic response of a large ventricular septal defect with a large left-to-right shunt, moderate to severe pulmonary hypertension, and moderately increased pulmonary vascular resistance (hyperkinetic pulmonary hypertension). The second type of response is characterized by insignificant change after the vasoactive drugs and is found in large defects with bidirectional shunt, severe pulmonary hypertension, and greatly elevated pulmonary vascular resistance (Eisenmenger's complex).

The purpose of this paper is to describe and analyze the mechanism of these differing responses. It is believed that the behavior of the murmur to these vasoactive drugs depends on the pulmonary vascular response, and this forms the basis of a pulmonary vascular function test.

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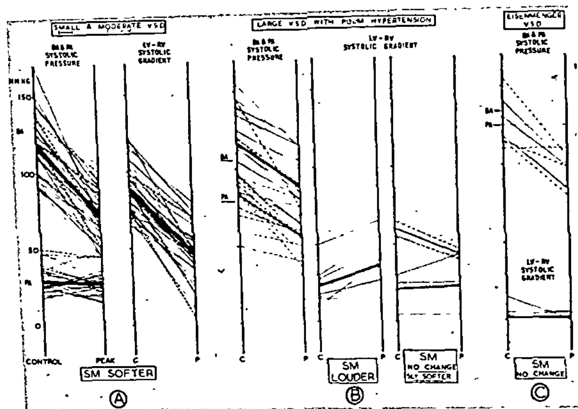


Fig. 1. The effect of amyl nitrite on the pulmonary and systemic systolic pressures and transseptal systolic gradient in VSD of different sizes *Group A:* Patients whose murmurs softened after amyl nitrite; the VSD was functionally small, with pulmonary systolic pressures under 50 mm Hg. The systemic systolic pressure fell much more than did the pulmonary pressure, thereby greatly reducing the transseptal systolic gradient The mean values are indicated by heavy lines. *Group B:* Patients whose murmurs either intensified, showed no change, or softened slightly; all had large VSD, with pulmonary systolic pressures above 50 mm. Hg. Note the marked drop in pulmonary systolic pressure (*first column*) When the murmur became louder (*second column*), the transseptal systolic gradient increased, because the fall in pulmonary pressure exceeded the fall in systemic pressure. When the murmur failed to change (*third column*), the gradient remained unchanged because both pressures fell equally; when it softened slightly, the gradient increased slightly, because the fall in systemic pressure exceeded the fall in pulmonary pressure. *Group C:* Patients with Eisenmenger's complex. Note the failure of the mean systolic gradient to change.

the case of a left-to-right shunt. When a right-to-left shunt emerges for the first time, or is shown to disappear or increase considerably, this can be interpreted as a change in the ratio of pulmonary to systemic resistance.

A phonocatheter was used in 23 patients of Group A, and 4 patients of Group B to demonstrate the existence of an intra-right-ventricular murmur and to study the effects of the vasoactive drugs on both internal and external murmurs, according to the technique previously described.[9]

Results

The subjects were arranged into three groups according to the response of the systolic murmur to the vasoactive drugs. The groups thus arranged were found to parallel closely the hemodynamic classification of VSD.

Response to amyl nitrite

In all patients studied, amyl nitrite produced a rapid fall in systemic blood pressure and tachycardia during the 20 to 30 seconds of inhalation and a return to normal after about 1 minute. The systolic murmur, however, behaved differently.

Group A. The usual response. The results shown graphically in Fig. 1,*A* indicate that when the systolic murmur softened markedly after amyl nitrite the control pulmonary systolic pressure was under 50

The state of the pulmonary vascular bed, whether normal, vasoconstricted, or the site of advanced secondary obliterative vascular disease, can thus be deduced. Since such knowledge is of vital importance in assessing the prognosis and predicting the response to surgical correction of the defects, these auscultatory and phonocardiographic tests may prove of value and interest.

Material and methods

A consecutive series of 57 patients with isolated ventricular septal defect (VSD) was studied. The material represented the full spectrum of VSD, but subjects who had a valvular or infundibular systolic gradient which exceeded 15 mm. Hg were excluded. The diagnosis was established by cardiac catheterization.

Amyl nitrite was administered to all and phenylephrine to most, and the change in the murmurs and heart sounds was always confirmed by recording sound tracings at fast paper speed according to the techniques previously described.[1-3] The tests were repeated during cardiac catheterization in order to correlate the change in murmur with the change in transseptal systolic pressure gradient. Pressures and sound tracings were usually recorded together with a dye-dilution curve and repeated during the height of the effect of amyl nitrite, as described elsewhere.[4]

After the pressures and murmurs had returned to the control level, pressure and sound recordings, with or without a dye-dilution curve, were repeated for the second control period. Phenylephrine was then injected slowly into the right side of the heart via the cardiac catheter, in a single dose which varied from 0.4 to 0.7 mg., until the systolic pressure had risen by at least 25 mm. Hg, whereupon the injection was discontinued. Pressures, sound recordings, and a dye-dilution curve were repeated, once sufficient hypertension and bradycardia had been produced. Pressure and sound recordings were continued for at least 5 minutes. In many subjects, amyl nitrite was again administered several minutes after the injection of phenylephrine, with the pressures subsiding, but still high.

All patients were studied in the supine position under sedation which consisted of either a mixture of pethidine, Phenergan, and Sparine in children, or a mild barbiturate in adults. Oxygen uptake was measured by the collection of expired air for a 3-minute period, and the gas content was analyzed by the micro-Scholander technique. Samples of blood for analysis of oxygen content (Van Slyke and Neill method) were taken simultaneously from the pulmonary artery and systemic artery during the collection of expired air.

Pulmonary vascular resistance was expressed in simple units.* However, the change in resistance during the peak action of the drugs used could not be estimated, because, with the techniques available, accurate measurements of pulmonary blood flow were impossible during the acute unsteady state and in the presence of a left-to-right shunt.

Left-to-right and right-to-left shunts were calculated from the saturation data and expressed as a percentage of pulmonary and of systemic flows, respectively. Similarly, the shunts estimated from dye-dilution curves were expressed as a percentage using the empirical formulae, devised by the Mayo Clinic group.[5]

Whereas changes in pressure and murmur could be accurately measured, determination of the changes in blood flow and vascular resistances presented a far more difficult problem, because of the short-lived unsteady state induced by these vasoactive drugs.[4,6-8] As discussed elsewhere,[4] the Fick method was clearly unsuitable for measuring pulmonary blood flow, nor could systemic dilution curves be used to measure blood flow in the presence of a left-to-right shunt. Because of the simultaneous change in systemic blood flow a change in the percentage left-to-right shunt was not synonymous with a change in shunt flow. However, the change in the right-to-left shunt was much easier to evaluate, since it is shown on the appearance slope and not as a distortion of the disappearance slope as in

$$^{*}\frac{\text{Mean pulmonary arterial pressure} - \text{Mean pulmonary wedge pressure}}{\text{Pulmonary blood flow (liters/minute)}}$$

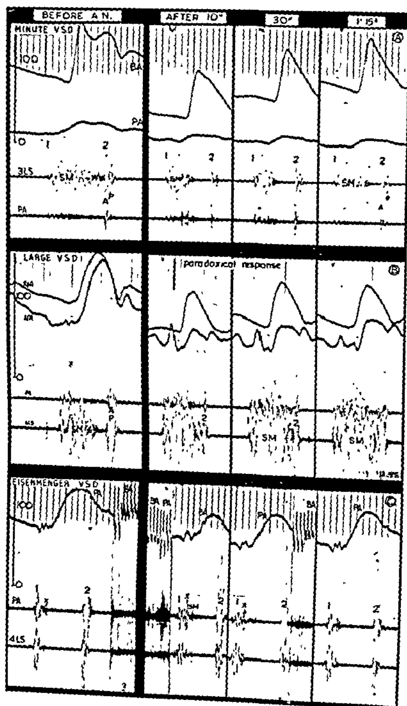


Fig. 3 The spectrum of responses to amyl nitrite. In minute VSD (*A*) the softening and shortening of the atypical systolic murmur accompanies the re- duced systolic gradient. In large VSD (*B*) the paradoxical intensification and lengthening of the *4LS* murmur closely parallels the increase in transseptal gradient because of the greater fall and slower recovery of the pulmonary sys- tolic pressure. The pulmonary ejection sound disappears and the second sound softens. In Eisenmenger's complex (*C*) no VSD murmur emerges, the pulmo- nary ejection sound and second sounds become slightly louder, and both sys- tolic pressures drop moderately and equally.

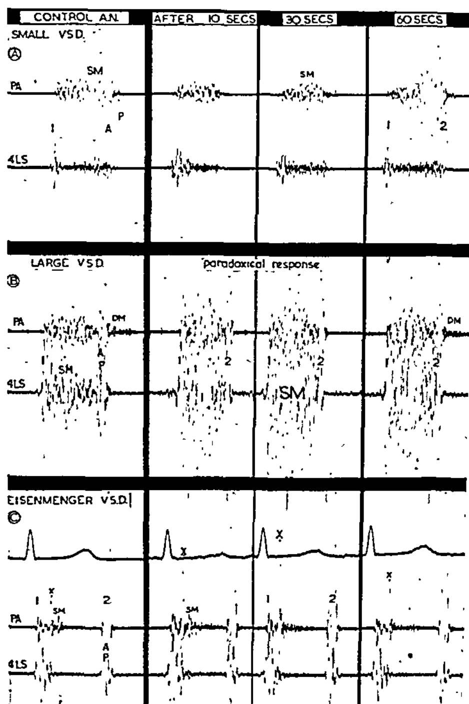


Fig. 2. The spectrum of responses of the systolic murmur to amyl nitrite. In small VSD (*A*) there is pronounced softening of the pansystolic murmur during the peak effect of amyl nitrite. In large VSD (*B*) the crescendo-decrescendo murmur intensifies and lengthens paradoxically, especially in the fourth left intercostal space (*4LS*), suggesting increased left-to-right shunt flow. The early diastolic murmur is temporarily abolished. In Eisenmenger's complex (*C*) there is no VSD systolic murmur before or after amyl nitrite; the murmur is probably a pulmonary ejection systolic murmur. The intensification of the pulmonary ejection sound (*X*) and failure of the second sound to soften suggest no appreciable fall in pulmonary pressure.

cating pulmonary hypertension (Figs. 3,*B* and 6). An apical mid-diastolic murmur was invariably heard, indicating a large left-to-right shunt. After amyl nitrite the systolic murmur intensified greatly and usually became pansystolic (Figs. 2,*B* and 3,*B*), which suggested marked increase in left-to-right shunt flow. That the change in the external murmur truly reflected intensification of the VSD murmur was shown by similar intensification of the intra-right-ventricular murmur (Fig. 4).

Amyl nitrite strikingly altered the *associated auscultatory signs*. Thus, the pulmonary ejection sound, when present, was always temporarily abolished, which suggested reduced pulmonary arterial pressure (Figs. 3,*B* and 6). Both components, especially the pulmonary, of the loud single or closely split second sound softened considerably, suggesting both systemic and pulmonary hypotension (Figs. 3,*B* and 5). An early diastolic murmur, present in 5 patients, was temporarily abolished in all (Figs. 2,*B* and 5). Since it was impossible to differentiate pulmonary incompetence from aortic incompetence or an associated patent ductus, the disappearance of the early diastolic murmur could reflect reduced systemic or pulmonary pressures (or both) induced by amyl nitrite.

Reliable *pressure data* were obtained in 14 patients when amyl nitrite was re-

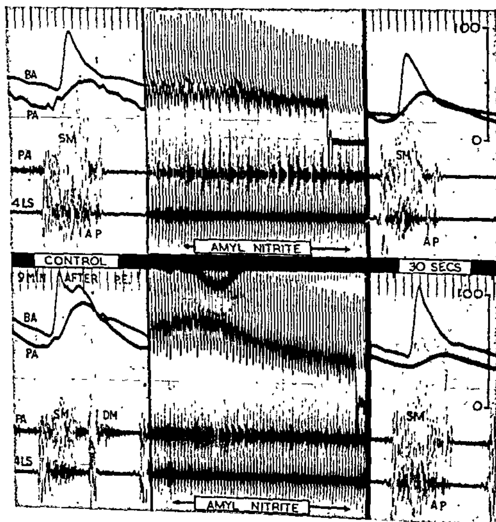


Fig. 5. The variation in the degree of paradoxical response to amyl nitrite in the same patient before and after "priming" the pulmonary vascular bed with phenylephrine. See text.

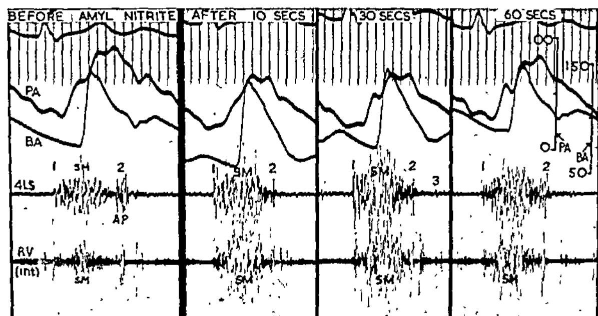


Fig. 4. The paradoxical response to amyl nitrite. The systolic murmur recorded within the right ventricle (*RV int*) is of a configuration similar to that of the external murmur at the *4LS*, and both murmurs intensify paradoxically after amyl nitrite. Note that the intensification of the murmur parallels the change in pulmonary systolic pressure, which is reduced more than the systemic pressure

mm. Hg. Of these, the defect was considered to be functionally small in 28 patients because the left-to-right shunt was under 50 per cent, and moderate in 4 because the shunt exceeded 50 per cent. In all the maximal softening, and often shortening, of the murmur occurred during the peak systemic hypotensive action of the vapor (Figs. 2,*A* and 3,*A*), at which point the gradient across the defect had been greatly reduced, presumably with resultant decrease in shunt flow.[1,2,3] The fall in pressure gradient was great because the pulmonary systolic pressure failed to change, whereas the systemic systolic pressure dropped precipitously, by an average of 43 mm. Hg (Fig. 1,*A*).

Group B. The paradoxical response. Instead of softening after amyl nitrite the *systolic murmur* promptly became louder in 13 of 19 patients, simulating the behavior of an ejection systolic murmur[1] (compare Figs. 2,*A* and 3,*A* with Figs. 2,*B* and 3,*B*). In 4 patients the murmur failed to change, and in 2 it softened slightly, but these 6 patients have been included in the group because their murmurs softened paradoxically after phenylephrine. All 19 had left-to-right shunts which exceeded 50 per cent, right ventricular systolic pressures which exceeded 50 mm. Hg, and slight to moderately elevated pulmonary vascular resistances (1.7-10; mean 5.1 units). In 13 the defect was shown to be large at operation; it ranged in diameter from 1 to 3.5 cm. (mean 2 cm.). The clinical and hemodynamic data are summarized in Fig. 11.

The systolic murmur was maximal in the third or fourth left intercostal space, of Grade 2 to 5 intensity, and, when loud, radiated widely, especially to the pulmonary area (Fig. 11). The severer the pulmonary hypertension the softer and shorter the murmur (Fig. 6). The configuration was always crescendo-decrescendo, with the crescendo in early or mid-systole. The decrescendo was rapid, so that the murmur often ceased at or just before the second sound. Although its shape closely simulated that of an ejection systolic murmur, the murmur was produced, in fact, at the site of the defect, as proved by recording a similar systolic murmur with a phonocatheter inside the right ventricle in 3 patients (Fig. 4). A pulmonary ejection sound and loud single or closely split second sound were usually recorded, indi-

close correlation between the intensity of the murmur and the transseptal peak systolic gradient is also evident in Figs. 4 and 5.

That the paradoxical response to amyl nitrite is related to the resting level of pulmonary hypertension is suggested by variations in the degree of response in the same patient tested under different circumstances. This was well shown in one subject. When amyl nitrite was first used, the child was excited and great paradoxical intensification of the murmur occurred (Fig. 2,*B*); however, during cardiac catheterization, when the patient was heavily sedated, the pulmonary systolic pressure was only 52 mm. Hg. Amyl nitrite now produced a slight softening of the systolic murmur, associated with a reduced systolic pressure gradient, because the drop in systemic pressure exceeded the trivial drop in pulmonary systolic pressure (Fig. 5, top section). Phenylephrine was then administered; it produced pulmonary hypertension and paradoxical softening of the murmur, presumably the result of its vasoconstrictive action on the pulmonary arterioles (*vide infra*). Nine minutes later the pulmonary systolic pressure of 85 mm. Hg was still much higher and the systolic murmur much softer than the control level (Fig. 5, bottom section). When amyl nitrite was again administered, a striking paradoxical intensification of the murmur occurred; it was now associated with a greater drop in pulmonary than systemic systolic pressure, with resultant widening of the peak systolic pressure gradient. The fact that the fall in pulmonary pressure preceded the fall in systemic pressure by about 4 seconds strongly suggested a direct vasodilatory action of amyl nitrite on the pulmonary resistance vessels. These observations suggest that the greater the degree of pulmonary vasoconstriction the greater the likelihood of paradoxical intensification of the murmur after amyl nitrite, provided that the vascular tone can be released.

Group C. Eisenmenger's complex. Unlike the findings in the group with a paradoxical response, a loud VSD systolic murmur failed to develop after amyl nitrite in 6 patients with Eisenmenger's complex, which is defined as large VSD with severe pulmonary hypertension, bidirectional shunting, and greatly elevated pulmonary vascular resistance (17 to 30 units). Five patients showed no increase in the soft ejection systolic murmur after inhalation of amyl nitrite (Figs. 2,*C* and 3,*C*), but in 1 patient a soft plateau pansystolic murmur emerged in the fourth intercostal space. This was attributed to transient tricuspid incompetence because of the shape and duration of the murmur and the intensification of the pulmonary ejection sound and second sound which suggested no fall in pulmonary arterial pressure. Necropsy a day after operation, which was performed elsewhere, showed complete closure of the septal defect; death was attributed to persistence of pulmonary hypertension.

In 2 patients with loud pulmonary regurgitant murmurs, amyl nitrite failed to soften the diastolic murmur, which suggested that little or no fall in pulmonary arterial pressure had occurred. This is in contrast to the disappearance of the early diastolic murmur in the group which showed paradoxical response. Again, unlike in the group which showed a paradoxical response, the pulmonary ejection sound and loud second heart sound failed to soften after amyl nitrite, but usually intensified (Figs. 2,*C* and 3,*C*).

The behavior of the *pulmonary and systemic pressures* after amyl nitrite was studied in 4 patients (Fig. 1,*C*). In 1 patient, neither pressure changed despite good inhalation; in 2, both the systemic and pulmonary systolic pressures dropped equally, and in the fourth subject the drop in systemic systolic pressure exceeded the drop in pulmonary pressure. The mean peak systolic gradient across the defect failed to change after amyl nitrite.

The effect of amyl nitrite on the *right-to-left shunt* was studied in 3 patients. In the first the right-to-left shunt increased after amyl nitrite when the femoral arterial oxygen saturation fell from 78 to 72 per cent; in the second there was no consistent change, and in the third the percentage right-to-left shunt diminished from 16 to 3 per cent. Had these patients responded like those of the paradoxical group, a diminution or disappearance of the right-to-left shunt might have been anticipated.

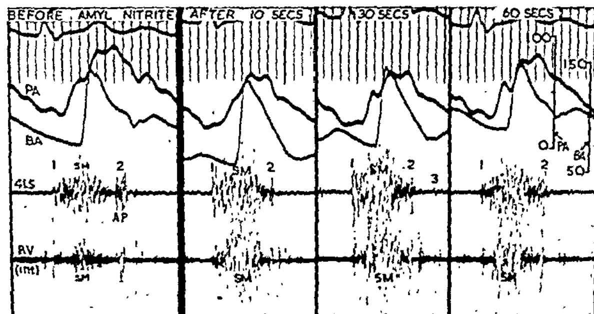


Fig. 4. The paradoxical response to amyl nitrite. The systolic murmur recorded within the right ventricle (*RV int*) is of a configuration similar to that of the external murmur at the *4LS*, and both murmurs intensify paradoxically after amyl nitrite. Note that the intensification of the murmur parallels the change in pulmonary systolic pressure, which is reduced more than the systemic pressure.

mm. Hg. Of these, the defect was considered to be functionally small in 28 patients because the left-to-right shunt was under 50 per cent, and moderate in 4 because the shunt exceeded 50 per cent. In all the maximal softening, and often shortening, of the murmur occurred during the peak systemic hypotensive action of the vapor (Figs. 2,*A* and 3,*A*), at which point the gradient across the defect had been greatly reduced, presumably with resultant decrease in shunt flow.[1,2,9] The fall in pressure gradient was great because the pulmonary systolic pressure failed to change, whereas the systemic systolic pressure dropped precipitously, by an average of 43 mm. Hg (Fig. 1,*A*).

Group B. The paradoxical response. Instead of softening after amyl nitrite the systolic murmur promptly became louder in 13 of 19 patients, simulating the behavior of an ejection systolic murmur[1] (compare Figs. 2,*A* and 3,*A* with Figs. 2,*B* and 3,*B*). In 4 patients the murmur failed to change, and in 2 it softened slightly, but these 6 patients have been included in the group because their murmurs softened paradoxically after phenylephrine. All 19 had left-to-right shunts which exceeded 50 per cent, right ventricular systolic pressures which exceeded 50 mm. Hg, and slight to moderately elevated pulmonary vascular resistances (1.7-10; mean 5.1 units). In 13 the defect was shown to be large at operation; it ranged in diameter from 1 to 3.5 cm. (mean 2 cm.). The clinical and hemodynamic data are summarized in Fig. 11.

The systolic murmur was maximal in the third or fourth left intercostal space, of Grade 2 to 5 intensity, and, when loud, radiated widely, especially to the pulmonary area (Fig. 11). The severer the pulmonary hypertension the softer and shorter the murmur (Fig. 6). The configuration was always crescendo-decrescendo, with the crescendo in early or mid-systole. The decrescendo was rapid, so that the murmur often ceased at or just before the second sound. Although its shape closely simulated that of an ejection systolic murmur, the murmur was produced, in fact, at the site of the defect, as proved by recording a similar systolic murmur with a phonocatheter inside the right ventricle in 3 patients (Fig. 4). A pulmonary ejection sound and loud single or closely split second sound were usually recorded, indi-

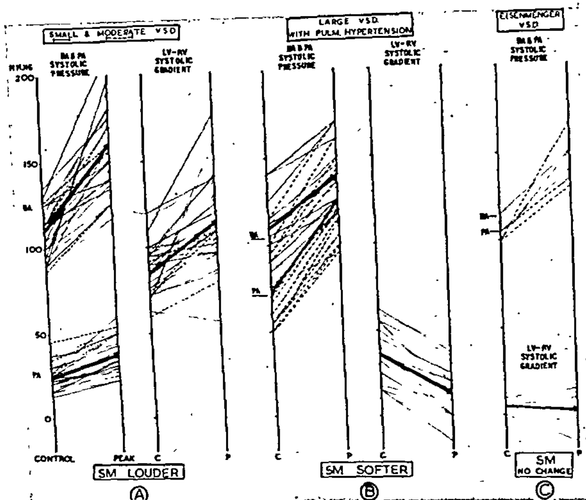


Fig. 7. The effect of phenylephrine on the pulmonary and systemic systolic pressures and transseptal systolic gradient in VSD of different sizes. *Group A:* Patients whose murmurs intensified after phenylephrine; the VSD was functionally small, with pulmonary systolic pressure under 50 mm. Hg The systemic systolic pressure rose much more than did the pulmonary pressure, thereby increasing the transseptal systolic gradient. Mean values are indicated by heavy lines. *Group B:* Patients whose murmurs softened. All had large VSD with pulmonary systolic pressures which exceeded 50 mm. Hg. The rise in pulmonary systolic pressure exceeded that of systemic pressure, thereby *reducing* the transseptal systolic gradient. *Group C:* Patients with Eisenmenger's complex. Note the failure of the transseptal systolic gradient to change significantly.

remained unaltered. However, after 1 minute the gradient lessened because the pulmonary systolic pressure continued to rise slowly while the systemic began to fall, whereupon delayed softening of the murmur ensued. This delayed type of paradoxical response probably represented the earliest stage in paradoxical behavior, since the 2 patients who showed it had the lowest resting pulmonary vascular resistances and pulmonary systolic pressures in the group, whereas those with higher pulmonary pressures and resistances all responded promptly to the drug. Fig. 9 shows that after phenylephrine was injected into the pulmonary artery, the rise in pulmonary arterial pressure preceded the rise in systemic pressure by about 4 seconds. This suggested a direct pulmonary vasoconstrictive response to the drug independent of the systemic circuit. Thereafter, the rise in pressure in the pulmonary circuit was greater and more abrupt than that in the systemic circuit. (Systemic systolic pressure rose from 136 to 170 mm. Hg, and pulmonary systolic pressure from 102 to 152 mm. Hg; thus, the peak systolic pressure difference fell from 34 to 18 mm.

Response to phenylephrine

After the intravenous injection of 0.4 to 0.7 mg. of phenylephrine, a rapid rise in systemic arterial pressure associated with bradycardia was observed in all patients studied, an action which persisted for some 3 minutes before gradually subsiding. The systolic murmur, however, behaved differently.

Group A. The usual response. The results shown graphically in Fig. 7,*A* indicate that, when the systolic murmur intensified after phenylephrine, the control pulmonary systolic pressure was under 50 mm. Hg. Of these, the size of the defect was considered to be functionally small in 28 and moderate in 4, for the afore-mentioned reasons stated for Group A. The systolic murmur intensified greatly in all, depending on the dose given and the individual variation (Fig. 8,*A*). The mean rise in pulmonary systolic pressure was only 14 mm. Hg, whereas the mean rise in systemic systolic pressure was 48 mm. Hg, thus increasing the mean difference in transseptal peak systolic pressures by 34 mm. Hg. (Fig. 7,*A*).

Group B. The paradoxical response. Instead of intensifying after phenylephrine, the systolic murmur became softer and orter (compare *A* and *B* of Fig. 8). Of the 19 patients who responded thus, the defects were considered to be large with large left-to-right shunts and hyperkinetic pulmonary hypertension (see data in Group B above and Fig. 11). In 3 patients the paradoxical response was weak and delayed; it began about 1 minute after the injection. In the rest the change in the murmur was immediate, commencing with the rise in systemic pressure and persisting throughout the 6 to 8 minutes of phenylephrine action. In 3 the VSD murmur was abolished, so that at the height of the paradoxical response the phonocardiographic appearance resembled that found in Eisenmenger's complex, namely, a loud delayed pulmonary ejection sound followed by a short soft ejection systolic murmur ending well before a very loud single second sound, representing synchronous closure of the intensified aortic and pulmonary components. That the change in the external murmur truly reflected softening of the VSD systolic murmur was shown by the similar reduction of the intra-right-ventricular murmur (Fig. 9). In 5 patients an *early diastolic murmur* in the pulmonary area intensified greatly after phenylephrine. Again it was not possible to distinguish pulmonary from aortic incompetence or associated patent ductus. The intensification implied a rise in aortic or pulmonary diastolic pressure or both (Fig. 5).

Systemic and pulmonary systolic pressure data were obtained in 14 patients, and the results are presented graphically in Fig. 7,*B*. The resting pulmonary systolic pressures ranged from 50 to 115 mm. Hg (mean 73), whereas the systemic systolic pressures ranged from 75 to 140 mm. Hg (mean 109). Comparison with resting pulmonary systolic pressures of Group A shows that about 50 mm. Hg appears to be the dividing line; when under this level the rise in pulmonary systolic pressure was slight and the murmur intensified, but when above this level the rise in pulmonary systolic pressure was very much pronounced and the murmur softened. The maximal rise in pulmonary systolic pressure exceeded that of the systemic pressure in all patients, resulting in a reduced peak systolic pressure difference across the defect. In 5 patients the rise in pulmonary systolic pressure was sufficient to abolish the gradient, and in 1 patient the pulmonary systolic pressure rose from a resting level of 15 mm. Hg below the systemic to 15 mm. Hg above the systemic, at which stage a right-to-left shunt was produced. The average reduction in the peak systolic pressure gradient was 23 mm. Hg, which is in striking contrast to the findings in Group A, wherein the pressure gradient increased by an average of 34 mm. Hg. This would seem to account adequately for the different behavior of the systolic murmur after phenylephrine in the two groups (compare *A* and *B* of Fig. 8).

In most patients the pulmonary arterial pressure rose promptly after phenylephrine, resulting in a rapid diminution of the peak systolic gradient and systolic murmur. In 2, however, the rise in pulmonary pressure was much slower, reaching a maximum only after about 1 minute. Until that stage the intensity of the murmur failed to change because the peak systolic gradient

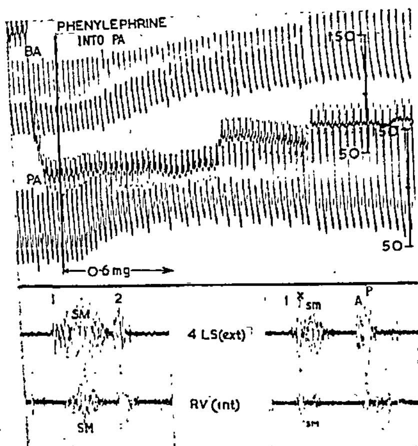


Fig 9. The paradoxical response after phenylephrine injected into the pulmonary artery. The external and intra-right-ventricular murmur both soften and shorten, which suggests reduced left-to-right shunt flow, whereas the *earlier*, greater, and more abrupt rise in the pulmonary arterial pressure probably indicates a direct pulmonary vasoconstrictive response which may exceed the systemic.

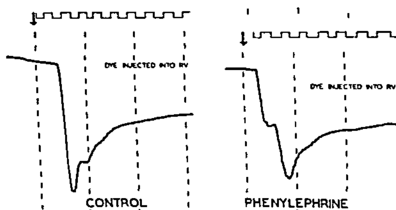


Fig. 10. Same patient as in Fig. 9, but dye-dilution curves recorded before and after another injection of 0 6 mg. of phenylephrine. The emergence of a 26 per cent right-to-left shunt during the peak action of phenylephrine indicates that the pulmonary vasoconstrictive response probably exceeded the systemic. Dye curves were recorded at a brachial artery after injection of the same dose of indocyanine green into the same site within the right ventricle.

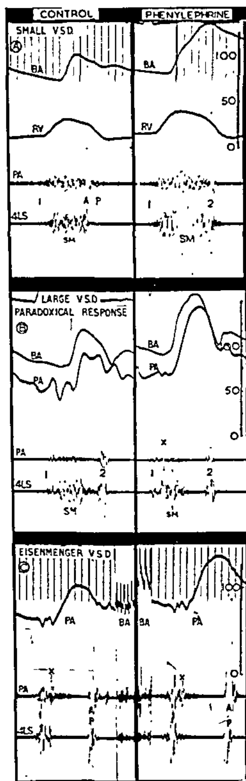


Fig. 8. (For legend see opposite column)

Hg.) This, together with the softened VSD systolic murmur, suggested that the pulmonary vasoconstrictive response exceeded the systemic response, with resultant great reduction in left-to-right shunt flow through the large defect.

In 5 patients, *right-to-left shunts* at the ventricular level, ranging from 6 to 25 per cent, emerged during the peak action of phenylephrine, as shown by the dye-dilution method. The appearance of such a shunt when not previously present must surely reflect a profound vasoconstrictive response of the pulmonary circulation to the drug, probably exceeding that of the systemic circulation (Fig. 10).

Group C. Eisenmenger's complex. Phenylephrine was administered to only 4 patients without producing any appreciable change in the sound tracings. This was not surprising since none had VSD systolic murmurs. The pulmonary ejection sound and pulmonary ejection systolic murmur were both softened slightly, probably due to reduced cardiac output after phenylephrine[4] (Fig. 8,*C*).

In 3 patients, in whom pressure recordings were obtained, phenylephrine markedly elevated the systolic pressures in both circuits; in 2 the rise in systemic pressure slightly exceeded the rise in pulmonary pressure, and in 1 the reverse occurred. There was no significant change in the mean peak systolic gradient across the defect (Fig. 7,*C*).

In 2 patients, right-to-left shunts of 14 and 23 per cent failed to change, in keeping with the virtually equal rise in the pulmonary and systemic pressures. In a third patient, in whom the pressures were not measured, the femoral arterial oxygen saturation rose from 73 to 80 per cent, which suggested a lessened right-to-left

Fig. 8. The spectrum of responses to phenylephrine. In small VSD (*A*) the great intensification of the pansystolic murmur is due to the increased transseptal systolic gradient, caused by the more powerful systemic pressor response. In large VSD (*B*) the paradoxical softening and shortening of the murmur (*4LS*) and emergence of a pulmonary ejection sound (*X*) reflects the striking pulmonary pressor response. Note the reduced peak systolic pressure gradient. In Eisenmenger's complex (*C*) both pressures rise equally, and the pulmonary ejection sound and second sound soften slightly.

seems much more likely that amyl nitrite reduces pulmonary vascular resistance to a greater degree than systemic vascular resistance, with resultant greater fall in pulmonary systolic pressure and increase in the left-to-right shunt. Conversely, phenylephrine was shown to elevate pulmonary arterial pressure and soften, shorten, and sometimes abolish the VSD systolic murmur. The greater the pulmonary pressor response the greater the softening of the murmur. Thus, it is believed that phenylephrine acts by causing pronounced pulmonary vasoconstriction with resultant severe pulmonary hypertension and diminished left-to-right shunt flow, and, at times, slight shunt reversal. Proof of these hypotheses must await measurements of the change in pulmonary vascular resistance and shunt flow. Such measurements were not possible in this study. However, it will be shown elsewhere that, in the presence of pulmonary hypertension associated with mitral stenosis, amyl nitrite is capable of reducing, and phenylephrine of greatly increasing, the pulmonary vascular resistance.[8] It is not unreasonable to anticipate an even greater pulmonary vasodilatory response in VSD with hyperkinetic pulmonary hypertension, wherein, because of the large left-to-right shunt, the concentration of amyl nitrite is likely to be much higher in the pulmonary circuit.

These differing responses of the murmurs to vasoactive drugs in VSD detracts considerably from the value of these drugs in differential diagnosis.[1] Their use in small VSD remains straightforward,[1,2] but confusion will be caused in the diagnosis of larger defects if the atypical and paradoxical responses are not appreciated. Fortunately, such defects are usually easily diagnosed by other parameters. The chief interest of the vasoactive drugs in VSD is now focused on their unique value as a bedside test of pulmonary vascular function. By this means the functional size and hemodynamic status can be more accurately evaluated in a given subject with VSD. Thus, when the murmur softens after amyl nitrite and intensifies after phenylephrine, a low-pressure pulmonary circuit with absent or weak responses can be predicted. Such patients will have functionally small or moderate-sized defects without pulmonary hypertension. When a loud VSD systolic murmur fails to change after these drugs, moderate systolic pulmonary hypertension (about 50 to 60 mm. Hg) is likely to be present. When the murmur behaves paradoxically to one or both of these drugs, a state of severe reactive pulmonary vasoconstriction is exposed, and a large VSD with hyperkinetic pulmonary hypertension can be predicted. Although the diagnosis of this type of VSD seldom presents much difficulty (Fig. 11), the paradoxical behavior of the murmur to the vasoactive drugs implies pronounced lability of the pulmonary vascular resistance and, therefore, a favorable prognostic indication that the pulmonary arterial pressure will fall after successful operation. That this inference is probably true has been borne out by our experience with 12 of these patients who were successfully operated on. In all, the right ventricular pressure fell promptly

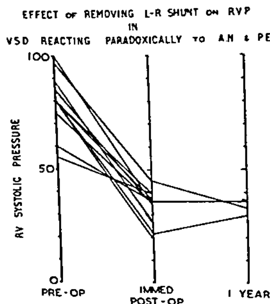


Fig. 12. The change in right ventricular systolic pressure immediately after successful closure of the VSD in 12 patients whose murmurs had responded paradoxically to the vasoactive drugs. The pressure fell to near normal or normal immediately on completion of the operation in all; and of the 3 who were recatheterized 1 year later, the pulmonary arterial pressure was slightly elevated in 2 (33/12 and 36/13 mm. Hg) and normal in 1 (27/11 mm. Hg), whereas the pulmonary vascular resistance ranged from 2.5 to 4 units

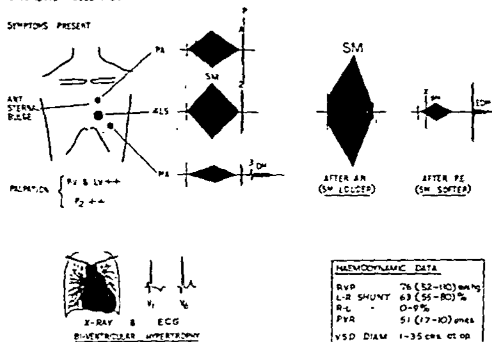


Fig. 11. Diagram depicting the clinical and hemodynamic findings in 19 patients whose systolic murmurs responded paradoxically to amyl nitrite and/or phenylephrine. All clinical parameters were characteristic of large VSD with hyperkinetic pulmonary hypertension. The VSD systolic murmur, loudest in the third or fourth left intercostal space, was always crescendo-decrescendo, ending at or before the loud single or closely split second sound. The severer the pulmonary hypertension the softer and shorter the murmur, and the more pronounced the paradoxical response to the vasoactive drugs. The VSD diameter at operation in 13 patients ranged from 1 to 3.5 cm. (mean 2 cm.)

shunt. These few observations suggest that, unlike in the group which had a paradoxical response, the pulmonary vascular response to phenylephrine did not exceed the systemic response.

Discussion

Variations in the response of the murmurs to amyl nitrite and phenylephrine in VSD without pulmonary stenosis seem to be dependent on the relative reactivity of the pulmonary and systemic resistance vessels. In functionally small and moderate-sized VSD without pulmonary hypertension, the changes in pulmonary arterial pressure are slight, whereas the changes in systemic pressure are much greater. The murmurs soften after amyl nitrite because the transseptal systolic gradient is much reduced by the marked fall in systemic pressure, whereas the pulmonary systolic pressure remains virtually unchanged. The murmurs intensify after phenylephrine because the gradient is greatly increased by the much greater pressor effect on the systemic circulation.

In large VSD with hyperkinetic pulmonary hypertension (in which instance the shunt flow is largely determined by the degree of pulmonary vasoconstriction), strikingly different effects are produced on the murmur and pulmonary arterial pressure. This appears to be due to the pronounced reactivity of the pulmonary resistance vessels to these drugs, not found in health[5,7] or in VSD without pulmonary hypertension. Amyl nitrite was shown to reduce the pulmonary arterial pressure and to intensify and lengthen the VSD systolic murmur. The greater the drop in pressure the greater the paradoxical intensification. Since intensification of the VSD murmur is believed to indicate increased left-to-right shunt flow,[2,4,5] the fall in pulmonary systolic pressure cannot be ascribed to reduced shunt flow. It

Summary

A study has been made to ascertain the reason for the variation in response of the systolic murmur to amyl nitrite and phenylephrine in VSD without pulmonary stenosis. The behavior of the murmur is believed to be determined by the degree of responsiveness of the pulmonary resistance vessels to these drugs, and this forms the basis of a unique pulmonary vascular function test in a patient with VSD.

When a VSD systolic murmur softens after amyl nitrite and intensifies after phenylephrine, a functionally small defect with a pulmonary systolic pressure under 50 mm. Hg can be diagnosed. The murmurs behave thus because the pulmonary vascular bed responds weakly (as in health), whereas the systemic resistance vessels react powerfully, resulting in a marked change in systolic gradient and, presumably, flow across the defect.

When a loud VSD systolic murmur fails to change after these drugs, a defect with a large left-to-right shunt and moderate pulmonary hypertension is likely to be present. The changes are equivocal because the pulmonary resistance vessels are believed to be more reactive than normal to the drugs, resulting in equal changes in pressure in the two circuits—hence, unchanged systolic gradient and, presumably, flow across the defect.

When a VSD systolic murmur intensifies after amyl nitrite and/or softens after phenylephrine, a large VSD with hyperkinetic pulmonary hypertension can be diagnosed. The murmur behaves paradoxically because the pulmonary resistance vessels, being endowed with excessive smooth muscle, are believed to respond powerfully to the drugs, with resultant pronounced changes in left-to-right shunt flow and murmur. The severer the pulmonary hypertension the more striking the paradoxical response. Amyl nitrite results in a greater fall in pulmonary than systemic systolic pressure and an intensified murmur which suggests increased left-to-right shunt flow, the result of greater reduction in pulmonary than systemic vascular resistance. Conversely, phenylephrine causes a greater rise in pulmonary then systemic systolic pressure and a softened murmur which suggests reduced left-to-right shunt flow due to the vasoconstrictive response of the pulmonary circulation exceeding that of the systemic.

The value of the paradoxical response is that it assures a labile pulmonary vascular resistance and, therefore, should be a favorable prognostic indication that the pulmonary arterial pressure will drop after operation.

The paradoxical response could not be elicited in Eisenmenger's complex, which suggests a relative lack of pulmonary vascular lability in this situation in which the very high resistance is usually the result of advanced obliterative pulmonary vascular disease.

We wish to thank members of the staff of Groote Schuur Hospital for referring cases for investigation, and the Superintendent, Dr. J. G. Burger, for his permission to publish. We gratefully acknowledge the assistance of Dr. C. Rainier-Pope and Dr. S. Esrachowitz, and that of our technicians, Mr. L. W. Piller, Mr. R. deMeneaud, Miss S. Joseph, and Miss A. Strauss. We also wish to thank the nursing staff and Mrs C. M. Hall for her secretarial assistance.

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to normal or near normal after closure of the defect (Fig. 12), which suggests that increased tone rather than advanced vascular changes accounted for the pulmonary hypertension of this group.

By contrast, on the basis of the failure of amyl nitrite to elicit a VSD systolic murmur and lessen the right-to-left shunt, a much less responsive pulmonary vascular bed was inferred to be present in the case of Eisenmenger's complex. This may be partially due to less concentration of amyl nitrite in the pulmonary circuit when the left-to-right shunt is small, but we prefer to ascribe the relative nonresponsiveness to a state of severe secondary, obliterative vascular disease with little vasoconstrictive factor. The pulmonary vasoconstrictive response to an intrapulmonary injection of phenylephrine likewise appeared to be less powerful than in the group with hyperkinetic pulmonary hypertension. The different degree of responsiveness to acetylcholine injected into the pulmonary artery is well known.[10,11] This drug causes a drop in the pulmonary arterial pressure in the group with hyperkinetic pulmonary hypertension, which indicates a release of tone in the resistance vessels,[12] whereas no such drop in pressure occurs in the group with Eisenmenger's complex.[11]

The presence or absence of a paradoxical response may prove to be of value in the subject with borderline Eisenmenger's complex. It is tempting to speculate that an operation would be contraindicated if amyl nitrite failed to bring out a VSD systolic murmur in a patient with a soft, short systolic murmur, signs of severe pulmonary hypertension, and slight cyanosis. Other adverse features would be failure of an associated pulmonary regurgitant murmur, pulmonary ejection sound, and right-to-left shunt to diminish or disappear. Unfortunately, our experience of its practical value is limited to only 2 patients. In the first (Fig. 6) the paradoxical intensification of the murmur was regarded as a favorable feature, and after operation the right ventricular systolic pressure fell from 80 to 40 mm. Hg. In the second, amyl nitrite failed to produce a VSD systolic murmur. The pulmonary resistance was 17 units, the left-to-right shunt was 10 per cent, and the right-to-left shunt was less than 10 per cent. The child died after closure of the defect.

There are well-described pathologic differences which may explain the differing responses to vasoactive drugs in subjects with VSD. In subjects with small defects without pulmonary hypertension the small pulmonary arteries and arterioles possess smooth muscle in the same modest amount found in healthy persons—hence, their weak reactivity to amyl nitrite and phenylephrine. When the VSD is wide enough not to obstruct transmission of systemic pressure into the pulmonary circuit, the volume of the shunt is determined by and is inversely proportional to the pulmonary vascular resistance. Since large septal defects embarrass the pulmonary circulation from birth, Edwards[13] and others[14] believe that the normal regression of smooth muscle in the fetal muscular pulmonary arteries and proximal segments of the arterioles is inhibited. These vessels continue to possess, or, if there is short-lived normal regression, acquire after the eighth week,[15] varying degrees of excessive smooth muscle, which maintains a state of increased tone in response to the elevated intraluminal pressure.[12] Being thus equipped with excessive smooth muscle, it is not surprising that they should be capable of as great reactivity as the systemic arterioles, or greater, to amyl nitrite and phenylephrine. Their reactivity to anoxia, oxygen administration, acetylcholine, Priscol, and other drugs has been recently reviewed by Fowler.[16] In the advanced case of pulmonary hypertension with greatly elevated pulmonary vascular resistance, progressive obliterative fibroelastic changes occur in the intima of the pulmonary arteries and progress to complete occlusion.[13,14] With the passage of time, extensive "dilatation lesions" develop, and it is not surprising that these rigid tubes with multiple blocks may be poorly reactive to vasoactive drugs.

A similar spectrum of response of the murmurs and pulmonary arterial pressures to amyl nitrite and phenylephrine has been found in patent ductus arteriosus.[17] This should be borne in mind when one endeavors to elicit a continuous murmur with pressor agents in subjects with a large ductus with atypical signs.

Effect of the Valsalva and Müller maneuvers on arterial oxygen saturation in normal subjects and in patients with congenital heart disease

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A simple diagnostic aid in the detection of left-to-right intracardiac shunts was thought to be available in the arterial oxygen responses to the Valsalva maneuver.[1] Lee and Gimlette,[1] using ear oximetry, observed falls in arterial oxygen saturation 2 to 3 seconds after cessation of airway straining in 26 patients with atrial septal defects, and this temporary arterial desaturation was explained as a shunt reversal during the first few seconds after the end of the Valsalva maneuver and mainly as a result of the sudden rise in net right atrial pressure. In 2 patients with atrial septal defects and cardiac failure, shunt reversal could not be demonstrated with the Valsalva maneuver, but it became apparent after effort or after the Müller test. McIlroy[2] found no shunt reversal in 21 patients with atrial septal defects who had a pulmonary to systemic mean flow ratio of 4.7 and a "square wave" Valsalva arterial pressure response. The same author also stressed that shunt reversal became more difficult with pulmonary to systemic mean flow ratios above 3.2.

However, arterial oxygen desaturation was observed in 34 patients who had atrial septal defects with low shunt flows and normal arterial pulse pressure responses to the Valsalva maneuver.

Jose and Milnor,[3] using direct cuvette recordings of arterial blood, were unable to distinguish between shunt reversals at the atrial level and the desaturation responses noted in normal subjects and in patients who had cardiovascular disorders without intracardiac shunts. They attributed a significant role for the arterial desaturations after the Valsalva maneuver in all their groups to normally occurring arteriovenous pulmonary shunts.

In the absence of agreement in regard to normal responses, those observed in patients with left-to-right shunts are calculated to be controversial. A systematic reappraisal of the changes in arterial oxygen saturation after the Valsalva and Müller maneuvers, therefore, seemed to be in order. In this study the normal swings of arterial oxygen saturation obtained during and after the Valsalva and Muller maneuvers were statistically analyzed and compared with those obtained in different types of acquired and congenital heart disease.

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Table I. *Arterial oxygen saturation during Valsalva maneuver (normal subjects)*

Subject	O_2 saturation at rest	% Change in saturation	
		Δ Rest + Phase 2	Δ Rest + Phase 4
1.	97	+1 0	+1 0
2.	97	+2.0	+2 0
3.	97	+1 0	+0 5
4.	100	0	0
5.	97	+3 0	+3 0
6.	94	−2 0	−3 0
7.	95	+5.0	+2 5
8.	97	0	0
9.	99	−6 0	−6 0
10.	99	0	0
11.	99	+1 0	0
12.	97	+2 0	+2 0
Mean	97.3	+0 7	+0 1
S.D.±	1 73		
		t_{11} = 29 0 p = > 0 001	t_{11} = 0 043 p = > 0 9

Mean time = 18 9 seconds. Mean pressure = 44 2 mm. Hg.

Table II. *Arterial oxygen saturation with Valsalva maneuver*

Subject	Condition	Arterial oxygen saturation		
		At rest	% Change in saturation	
			Δ Rest + Phase 2	Δ Rest + Phase 4
6. Mean S D ±	Rheumatic aortic valve disease	96 3 1 1	+1 9	−0 3
4. Mean S D.±	Emphysema	92 3 2 6	+1 1	+1.6
5. Mean S D ±	Rheumatic mitral valve disease	95 0 2 1	+1 0	−0.2
5. Mean S D.±	Hypertension	94 8 2 1	+0 7	+1.3
7. Mean S D.±	Miscellaneous diseases	96 7 1 4	+1.3	+1.6
			t_{17} = 0.3074 p = > 0.7	t_{17} = 1.286 p = > 0.2

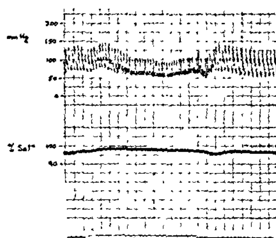


Fig. 1. Patient L. R., normal subject. Effect of Valsalva maneuver on arterial blood pressure and arterial oxygen saturation. Speed 2.5 mm. per second; strain pressure 40-70 mm. Hg. The period of strain is represented by the broad rectangular line on the time line.

Material

The 56 patients studied comprised four main groups: *Group 1*—12 patients without cardiorespiratory disease; *Group 2*—10 patients with atrial septal defect proved during cardiac catheterization; *Group 3*—7 patients with congenital heart disease other than atrial septal defects, established during routine cardiac catheterization; and *Group 4*—27 patients with a variety of acquired cardiopulmonary diseases.

Method

Ear oximetry was used for the purpose of recording rapid changes in saturation rather than precise levels of arterial oxygen saturations. The instrument used was a dual single-scale oximeter,* a modification of that described by Wood and associates,[4] which permits for direct readings on the dual galvanometer assembly of Waters or for continuous records of arterial oxygen saturation on a direct-writing recorder.† Prior to each study the oximeter was calibrated against known blanks to provide a 1-mm. deflection for a 1 per cent change in saturation within the range of 70 to 100 per cent. The instrument was attached to the pinna, and adjustments were made for thickness of the ear and drift during warming of the ear. After about 2 minutes, ambient readings were taken, and checks made for directional changes during short periods of apnea and oxygen breathing.

The Valsalva maneuver was carried out by means of a forced expiration from the end-expiratory level against a mercury manometer pressure of 40 mm. An airway strain was so maintained for a period of 15 to 20 seconds. For the Müller test the patient was instructed to exert a similar suction pressure for the same period from the resting expiratory level and through a mouthpiece connected to the mercury manometer. Simultaneously, arterial oxygen saturations by oximetry and arterial blood pressure from an indwelling arterial needle were inscribed on the direct-writing recorder.

Results

Normal arterial oxygen saturation responses to Valsalva maneuver (Fig. 1). The arterial oxygen saturation responses of 12 normal subjects are summarized in Table I. A mean strain pressure of 44.2 mm. Hg was maintained for an average of 18.9 seconds. The mean oxygen saturation of arterial blood at rest was 97.3 per cent. During the strain pressure the saturation rose by a mean of 0.7 per cent, and 3 seconds after release of the strain the saturation stayed above the resting level by a mean of 0.1 per cent. Although the rise during Phase 2 is statistically significant ($p = >0.001$), no significant difference exists between the ambient and post-Valsalva arterial oxygen saturations ($p = >0.9$).

A mean fall in pulse pressure of 36.2 mm. Hg in Phase 2 is associated with the mean rise of 0.7 per cent in saturation; and a mean rise in pulse pressure of 29.6 mm. Hg in the first 3 seconds of Phase 4 accompanies the mean rise of 0.1 per cent in saturation.

The general rise in oxygen saturation 8 or more seconds after release of strain pressure coincides with the usual hyperpnea and will not be considered further.

The changes in mean arterial oxygen saturation during Phases 2 and 4 in 27 hospital patients are shown in Table II.

*Waters Conley Company, Rochester, Minn.
†Sanborn Company, Waltham, Mass.

levels in Phases 2 and 4 ($p = > 0.1$ for both Phases 2 and 4).

Responses to Valsalva maneuver in atrial septal defects (*Fig. 3*). Table IV analyzes the mean pulse pressures observed in patients with atrial septal defects (ASD) as contrasted with those in normal subjects. All patients with ASD were free from congestive heart failure, and the mean pulmonary to systemic flow ratio in 4 was 2.6. Variation from the normal mean pulse pressure responses to the Valsalva

Table III. Arterial oxygen saturation during "square wave" responses with Valsalva maneuver

Subject	Diagnosis	Arterial pulse response	Strain		Arterial oxygen saturation			% Change in saturation	
			Pressure (mm.Hg)	Time (sec.)	Rest	Phase 2	Phase 4 (3 sec)	Rest + Phase 2	Rest + Phase 4
6.	Atrial septal defect (3) Rheumatic heart disease (3)	Square wave Square wave							
Mean			40	16	93.4	94.1	93.7	+0 5	+0.1
S.D.±			0	2	4.2	4 0	4 6		
								$t_5 = 2.1$ $p = > 0.1$	$t_5 = 2.1$ $p = > 0.1$

Table IV. Variation of pulse pressure and arterial oxygen saturation during Valsalva maneuver in normal subjects and patients with atrial septal defects

Subject	Condition	Valsalva response	Resting oxygen saturation	Pulse pressure (mm. Hg)					Change in oxygen saturation	
				At rest	Phase 2	Phase 4	Δ Rest + Phase 2	Δ Rest + Phase 4	Δ Rest + Phase 2	Δ Rest + Phase 4
12.	Normal	Normal arterial pressure response								
Mean			97.3	48.7	12 5	78 3	−36.2	+29 6	+0.7	+0.1
S.D.±			1.73	9.09	2.72	16.3	9.07	13.7		
6.	Atrial septal	Overshoot present								
Mean			93.0	48 3	37.5	79.0	−10 8	+30.7	+1.3	−5.3
S D ±			3.5	16.4	13.1	27.4		14 0	0	3.7
							$t = 3.067$ $p = > 0.01$	$t = 4.905$ $p = < 0.001$	$t_5 = 13.154$ $p = < .001$	$t_5 = 5 0$ $p = 0.01$
3.	Atrial septal defect	Square wave								
Mean			93 7	44.6	41.3	45	3.3	3	+0.7	+0.1
S.D.±			4.7	5.0	8.1	8.6			$t_2 = 2.12$ $p = > 0.1$	$t_2 = 2.1$ $p = > 0.1$
							Comparison of patient with overshoot ASD and normal subjects		$t_{16} = 0 504$ $p = 0 6$	$t_{16} = 4.804$ $p = 0.001$

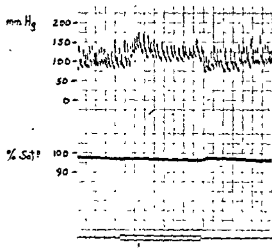


Fig 2. Patient H. L., in congestive heart failure. A square wave pulse response to the Valsalva maneuver. The arterial oxygen saturation after strain remains unchanged. Speed 2.5 mm. per second; strain pressure 40 mm. Hg. The period of strain is represented by the broad rectangular line on the time line.

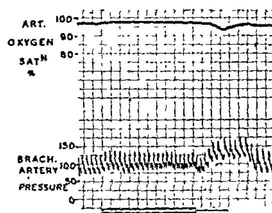


Fig. 3. Patient M.A.B., with atrial septal defect. Normal pulse pattern and significant drop in arterial saturation after the Valsalva maneuver. Speed 2.5 mm. per second; pressure in millimeters of mercury. The period of strain is represented by the broad rectangular line on the time line.

The diagnoses permitted five main subdivisions. Group 5 included patients with tabes dorsalis, hyperthyroidism, and Paget's disease of the bone. These patients were not in heart failure, and none showed in their arterial pulse contour a "square wave" response to the Valsalva maneuver.

In Group 1, patients with rheumatic aortic valve disease, a mean strain pressure of 44 mm. Hg was maintained for 21 seconds. There was a mean rise of 1.9 per cent during the strain pressure, and a mean fall of 0.3 per cent after release of the strain.

In Group 2, patients with advanced respiratory disease, a mean strain pressure of 40 mm. Hg was exerted for 12.8 seconds. This resulted in a mean rise in arterial oxygen saturation of 1.1 per cent during the strain period, and a mean rise of 1.6 per cent during the overshoot.

In Group 3, patients with rheumatic mitral valve disease, a mean pressure of 53.0 mm. Hg was exerted for 14.4 seconds, which caused a mean rise in arterial saturation of 1.0 per cent during the strain and a fall of 0.2 per cent after its release.

In 5 patients with hypertension of Group 4, a mean rise of 1.3 per cent followed the cessation of strain. The results were similar in Group 5. Here a mean strain pressure of 39 mm. Hg was exerted for 14.4 seconds. Mean rises in arterial saturation of 1.3 and 1.6 per cent ensued during and after the strain period, respectively. The rise in saturation during Phase 2 in this group is the same as that seen in the normal group; there was *no* difference between them ($p = >0.7$). Similarly, the saturations in Phase 4 are similar to those of the normal group and are not significantly different from the ambient values ($p = 0.2$).

Thus, both groups showed significant rises in saturation in Phase 2, whereas 3 seconds after release of airway straining the saturation did not significantly deviate from the ambient level.

Changes in arterial oxygen saturation with Valsalva maneuver in presence of a "square wave" response (Fig. 2). Three patients with atrial septal defects who were not in heart failure, and 3 patients with rheumatic heart disease who were in congestive heart failure showed typical "square wave" responses in their arterial pulse contours, namely, elevation both in systolic and diastolic pressure during airway straining, extinction of the overshoot, and a total absence of bradycardia in Phase 4. The mean pulmonary to systemic flow ratio in 2 of these patients with atrial septal defects was 3.5.

Table III shows that arterial oxygen saturations in this "square wave" group did not differ significantly from the resting

Apart from the difference in pulse pressure response the arterial oxygen saturation differences in patients with ASD are of particular interest (Table IV). In 6 subjects with ASD who had a normal overshoot a significant drop in saturation, which varied from 2.0 to 13.0 per cent (mean 5.5 per cent), occurred on cessation of strain pressure. In contrast to the findings in normal subjects, this fall was highly significant statistically ($p = 0.001$), whereas the temporary elevation in saturation of 1.3 per cent during Phase 2 was not significant ($p = 0.6$) when contrasted with that found in the normal subjects.

Responses to Valsalva maneuver in other congenital heart diseases (Figs. 4 and 5). The responses of patients with other forms of congenital heart disease to the Valsalva maneuver are summarized in Table V. These patients, including one with a ventricular septal defect (VSD), one with pulmonary stenosis, and 2 with patent ductus arteriosus, showed no drop in arterial saturation after the strain period. One patient with VSD who showed a drop of 0.5 per cent in saturation had an arterial pressure response of the square wave type. The patient with tetralogy of Fallot showed a continuous fall in saturation throughout the strain period, and a further 5 per cent fall during a normal overshoot. One patient with Ebstein's disease showed a square wave arterial response with a rise in saturation of 2 per cent during Phase 2, and a fall of 8.5 per cent in saturation after release of strain pressure. This is the only example in this study of a patient with a square wave response who also unequivocally desaturated at the end of the Valsalva maneuver.

Normal response to Müller maneuver. The arterial oxygen saturation during the Müller maneuver falls steadily throughout the suction period and reaches its lowest point 3 seconds after cessation of suction. This is followed by a sharp rise over the next 6 to 8 seconds, coinciding with hyperpnea.

In 9 normal subjects the mean suction pressure was 47.2 mm. Hg over a mean time of 16.1 seconds. The mean drop in saturation was 8.7 per cent at 3.2 seconds after cessation of the suction pressure, and 6.2 per cent of this desaturation occurred during the suction period. The arterial saturation rose to a mean of 98.8 per cent 7.6 seconds after the lowest saturation occurred, i.e., 1.2 per cent above the saturation observed at rest. The post-Muller fall in saturation in this normal group is highly significant statistically ($p = 0.001$).

The changes in arterial oxygen saturation induced by the Müller maneuver in 11 subjects with miscellaneous diseases, including emphysema, rheumatic mitral and aortic heart disease, were similar to those seen in normal subjects (Table VI).

A mean desaturation of 5.5 per cent

Table V. Arterial oxygen saturation with Valsalva maneuver in patients with congenital heart disease

Subject	Condition	Valsalva response	Arterial oxygen saturation		
			At rest	% Change in saturation	
				Δ Rest + Phase 2	Δ Rest + Phase 4
R.McF.	Ebstein's disease	Square wave	96	+2.0	−8.5
B.J.S.	Tetralogy of Fallot	Normal	93	−9.0	−16.0
R.B.	VSD	Square wave	99	+0.5	−0.5
D.B.	VSD	Normal	96	+1.0	0
C.H.	Pulmonary stenosis	Normal	92	0	0
H.L.	PDA	Normal	97	+1.0	0
T.McL.	PDA	Normal	96	−0.5	0

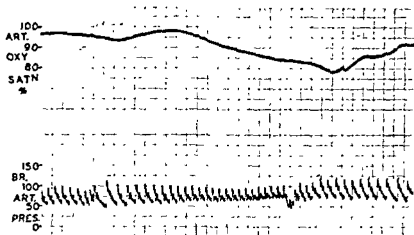


Fig. 4. Patient B.J.S., with tetralogy of Fallot. The pulse pressure pattern is normal and the oxygen saturation falls progressively throughout Phases 2, 3, and 4 of the Valsalva maneuver. Speed 5 mm. per second; pressure in millimeters of mercury. The period of strain is represented by the broad rectangular line on the time line.

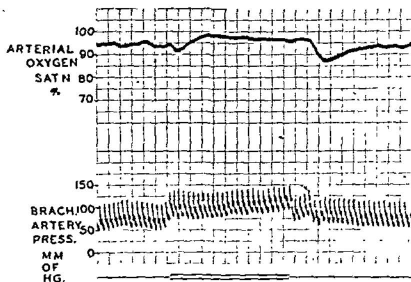


Fig. 5. Patient R.McF., with Ebstein's disease. A "square wave" pulse pressure pattern and desaturation after release of the airway straining. Speed 2.5 mm. per second. The period of strain is represented by the broad rectangular line on the time line.

maneuver is seen in Phases 2 and 4. Three patients showed frank "square wave" responses. The mean fall in pulse pressure in Phase 2 in the normal subjects was −36.2 mm. Hg, whereas in the 6 patients with ASD who had a normal pressure response the corresponding mean fall in pulse pressure in Phase 2 was only 10.8 mm. Hg.

A difference in mean pulse pressure response exists also during the overshoot. The mean rise in pulse pressure in the normal subjects during the overshoot was 29.6 mm. Hg, whereas in the 6 subjects with ASD a mean rise of 30.7 mm. Hg occurred. These differences in pulse pressure between that at rest and that in Phases 2 and 4 in these two groups are statistically significant ($p = 0.01$ and 0.001, respectively).

seconds after release of suction. A drop of 5.8 per cent was effected during the maintenance of decreased intrathoracic pressure. The falls in saturation after the Müller maneuver differ significantly ($p = 0.01$) from the resting values, but, quantitatively, the falls do not differ from the values in the normal subjects ($p = 0.8$).

The suction pressure exerted in the normal subjects and in patients with ASD was 47 mm. Hg, although the mean time of suction in the patients with ASD exceeded that of the normal subjects by 4.6 seconds; the rates of fall in saturation were 0.46 and 0.40 per cent per second for the normal subjects and the patients with ASD, respectively.

The Müller maneuver, therefore, produced a pattern of consistent desaturation which began during the period of increased negative intrathoracic pressure, continued for some 3 seconds after suction pressure ceased, and then returned to above normal levels in 6 to 10 seconds. This pattern occurred in normal subjects as well as in patients with a variety of diseases, including ASD, and a significant difference between the responses of these groups could not be established (Fig. 6).

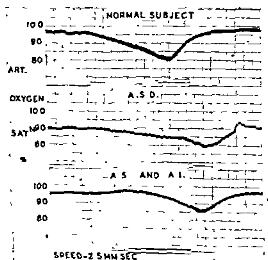


Fig. 6. Behavior of arterial oxygen saturation in a normal subject (*top*), in a patient with atrial septal defect (*center*), and in a patient with aortic valve disease (*bottom*), during and after the Müller maneuver. Speed 2.5 mm. per second. The period of strain is represented by the broad rectangular line on the base line.

Discussion

Significant arterial oxygen desaturation followed the release of the Valsalva strain pressure in only 6 of the 10 patients with atrial septal defects in the present study. This response distinguishes these patients from normal subjects and confirms in part the observation of Lee and Gimlette.[1] This shunt reversal follows the sudden release of the venous return, partially throttled during the Valsalva maneuver,[5,6] which surges back into the right atrium and elevates its pressure. For a short period during the overshoot, right atrial pressure exceeds that of the left, and venous blood enters the left heart across the atrial septal defect, provided that it is not too large.[2] In patients with atrial septal defects who have high pulmonary to systemic mean flow ratios, airway straining does not raise net right atrial pressure, arterial desaturation is absent, and a square wave blood pressure pattern emerges in the absence of heart failure.[2,7] The ambient mean right atrial pressure in these 3 patients with atrial septal defects was 12.5 mm. Hg, as contrasted with 5.5 mm. Hg in the group of 6 who showed a normal response. This elevation in ambient right atrial pressure presumably precludes effective throttling of the venous return, and high right ventricular stroke volumes are maintained in spite of airway straining. In this series, 3 patients with ASD who were not in failure showed this pulse pattern and did not desaturate. Similarly, 3 patients who were in congestive heart failure, and who had no intracardiac shunts, showed the square wave pulse response and failure to lower arterial oxygen saturation after the Valsalva maneuver; in that respect, these "square wave" patients resembled the normal patients.

The significant elevation in arterial oxygen saturation during the strain period was common to both the normal and ASD groups. This has been described previously[1,2] and attributed to a temporary elevation of alveolar pO_2; the latter depends on the actual magnitude of strain pressure and its duration.[8] In this study, a fall in saturation during the strain period was found only in patients with Fallot's tetralogy. Desaturation at the end of the

Table VI. Arterial oxygen saturation with Müller maneuver in subjects with miscellaneous diseases

Subject	Condition	Arterial oxygen saturation										
		Suction		During suction			Post-Müller				% Change in saturation	
		Pressure (mm. Hg)	Time (sec.)	At rest	Onset	End	Lowest	Time (sec.)	Highest	Time (sec.)	Δ Rest + End of strain	Δ Rest + Post-Müller
9.	Normal											
Mean		47.2	16.1	97.6	97.7	91.3	88.7	3.2	98.8	7.6	−6.2	−8.7
S.D.±		12.5	6.3	0.7	2 05	4.6	4.73	0.6	2.6	0.8	4.0	4.2
												t_8 = 9.75 p = < 0.001
11.	Miscellaneous											
Mean		51.7	18	95.5	95.7	90.1	87.5	4.5	96.4	10.5	−5.5	−8.1
S D.±		18.6	4 0	1.9	2.2	5.2	5.7	1.5	2.0	7.2		

Pooled variance of miscellaneous compared with normal post-Müller — t_{10} = 0 0235, p = 0.90

Table VII. Arterial oxygen saturation with Müller maneuver in patients with ASD

Subject	Condition	Arterial oxygen saturation										
		Suction		During suction			Post-Müller				% Change in saturation	
		Pressure (mm. Hg)	Time (sec.)	At rest	Onset	End	Lowest	Time (sec.)	Highest	Time (sec.)	Δ Rest + End of strain	Δ Rest + Post-Müller
6.	Atrial septal defect											
Mean		46 6	19.7	90	90 5	84.7	81	4.3	92	8.7	−5.8	−9.5
S.D.±		20	7.6	5	5 8	4.4	5.2	1.5	3.6	1.6	2.3	2.8
												t_6 = 4.032 p = < 0.01

Pooled variance post-Müller ASD compared with normal — t_{12} = 0.1973, p = > 0 8

occurred at a mean suction pressure of 51 mm. Hg over an average of 18 seconds. A mean fall in saturation of 8.1 per cent was reached after a mean of 4.5 seconds after cessation of strain.

The mean maximum fall in saturation is highly significant statistically (p = 0.001) in this group also and does not differ from that seen in normal subjects (p = 0.9).

Response to Müller maneuver in atrial septal defects. The changes in arterial oxygen saturation induced in 6 patients with ASD who had normal pulse pressure responses during the Valsalva maneuver are shown in Table VII. A mean suction pressure of 46.6 mm. Hg was sustained for an average of 19.7 seconds, and a mean desaturation of 9.5 per cent occurred 4.3

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strain period and in the presence of a square wave response distinguished the patient with Ebstein's disease.

Arterial oxygen desaturation effected by the Müller maneuver has been thought to distinguish patients with atrial septal defect in heart failure from those free from failure.[1] Studies which concern the effect of the Müller maneuver on arterial oxygen saturation in normal individuals are lacking, and the observations of the present series indicate that desaturation in excess of 8 per cent follows the cessation of suction pressure in all subjects, irrespective of diagnosis, and a statistical difference does not exist between the falls in arterial oxygen saturation of normal individuals and those of patients with ASD.

The hemodynamic changes induced by the Müller maneuver are not fully known, but there is some evidence which indicates that a negative intrathoracic pressure of 18 to 22 mm. Hg increases the cardiac index 1.13 L./min./M.[2], and that stroke volume rises by a mean of 27.1 ml. above a resting level of 68.3 ml.[10,11]

In addition to this elevation in cardiac output, during a sustained rise in negative intrathoracic pressure the functional residual capacity diminishes as a result of an increase in pulmonary blood volume, which is approximately 200 to 500 ml.[12] These changes, apnea and the small reduction in alveolar partial pressure of oxygen, are calculated to deplete the oxygen store in the lungs and lower the alveolar-arterial oxygen gradient. The combination of these factors leads to a steady desaturation of arterial blood during, and for the approximate 3.5 seconds after, the Müller maneuver.

The rate of fall in saturation is of some interest, inasmuch as a fall in saturation of 0.46 per cent per second in the normal subjects was slightly higher than the fall of 0.4 per cent per second found in the patients with ASD at a similar suction pressure. The desaturation during the Müller maneuver in the patients with ASD is unlikely, therefore, to be the result of a shunt reversal across the defect. In view of the essentially similar effect on arterial oxygen saturation in all groups studied, the Müller maneuver fails to distinguish between them.

Summary

The arterial oxygen saturation was measured by oximetry during the Valsalva and Müller maneuvers in 56 patients. In 12 normal patients the mean resting arterial oxygen saturation was 97.3 per cent (S.D. ± 1.7 per cent). During the strain period (Phase 2) the mean arterial oxygen saturation rose slightly to 97.9 per cent (S.D. ± 2.7 per cent) ($p = >0.001$); and after release of the strain pressure it returned to ambient levels (Phase 4), 97.5 per cent (S.D. ± 2.7 per cent) ($p = >0.9$).

Essentially similar results were obtained in 27 patients with varieties of acquired heart disease.

In patients with atrial septal defects (ASD) the mean resting arterial oxygen saturation was 93.0 per cent (S.D. ± 3.5 per cent), and during the strain period the mean arterial saturation rose to 94.3 per cent (S.D. ± 4.5 per cent) ($p = <.001$). The mean desaturations observed in 6 patients with ASD at the end of the strain period (Phase 4) was 5.3 per cent (S.D. ± 3.7 per cent) ($p = 0.01$). Desaturations were absent in 3 patients with atrial septal defects at the end of the strain period, and in 3 patients who showed a "square wave" response in their arterial pulse tracing.

The normal mean resting arterial oxygen saturation with the Müller maneuver was 97.6. At the end of the suction period the mean fall in oxygen saturation in normal subjects was 8.7 per cent (S.D. ± 4.1 per cent) ($p = <0.001$).

The mean resting oxygen saturation in patients with ASD during the Müller maneuver was 97.0 per cent, and the mean fall at the end of the suction period in these patients was 9.5 per cent (S.D. ± 2.8 per cent).

These observations showed that: (1) The Valsalva maneuver reduces arterial oxygen saturation in patients with atrial septal defects whose pulse pattern response is normal. (2) The Müller maneuver has no value in the detection of right-to-left shunts at the atrial level, inasmuch as desaturation occurred in all patients irrespective of diagnosis.

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clinical grounds, with compatible electrocardiograms and x-ray findings. In 3 patients the diagnosis was confirmed at operation, and in 3, at autopsy. One of the latter had an atrial septal defect in addition to a tetralogy.

Seven patients had a patent ductus arteriosus. In 1 the diagnosis was made because of the presence of a typical continuous murmur, with compatible x-ray and electrocardiographic findings. In the other 6 patients the diagnosis was confirmed at the time of operation. In addition to a patent ductus, 1 patient had a ventricular septal defect and coarctation of the aorta.

Three adults had endocarditis on the aortic valve. All had had murmurs of aortic stenosis since infancy. In 1 the diagnosis was confirmed at operation.

Valvular pulmonic stenosis was diagnosed in 1 patient by cardiac catheterization; and infundibular pulmonic stenosis was proved at operation in another.

One patient had endocarditis at the site of a coarctation of the aorta; this was discovered at autopsy.

Two patients had a variant of a truncus arteriosus. In 1 the diagnosis was made by angiocardiography, and the other developed endocarditis about 6 months after surgical correction of an aorta–pulmonary artery window.

A 7-year-old white girl died of endocarditis which involved a normal aortic valve, and was thought, at autopsy, to have had fibroelastosis.

Duration of symptoms. Fourteen patients had symptoms less than 4 weeks prior to diagnosis. Twenty-four had symptoms longer than 4 weeks.

Symptoms and signs. All patients presented with fever and malaise. In 15 (40 per cent), this was the only complaint. Eight (21 per cent) had, in addition, symptoms of respiratory infection, which ranged from sinusitis to pleuritic chest pain. Seven (18 per cent) had symptoms of congestive heart failure. Five (13 per cent) presented with symptoms secondary to emboli: to the central nervous system in 3, to the kidney in 1, and to the brachial artery in 1. Two patients had rash and fever; 1 patient complained of fever, malaise, and diarrhea.

During the illness, 30 patients (79 per cent) were found to have splenomegaly; 17 (45 per cent), embolic phenomena; 14 (37 per cent), congestive heart failure; 10 (26 per cent), clubbing (8 of these had right-to-left shunts); 10 (26 per cent), petechiae; and 8 (21 per cent), heart failure and embolic phenomena. These signs were not always present on admission, but developed sometime during the course of the illness. In 8 patients (21 per cent), neither clubbing, petechiae nor splenomegaly was present.

The murmurs present were usually those of the underlying congenital anomaly. In 2 patients, one with aortic stenosis and another with aorta–pulmonary artery window, diastolic murmurs developed during treatment.

Laboratory findings.

ANEMIA. The hemoglobin concentration ranged from 8.3 to 20.6 Gm. per cent. Of 35 patients in whom the hemoglobin concentration was known, 20 (57 per cent) were anemic.

WHITE BLOOD CELL COUNT. Forty-four per cent of 36 patients had white blood cell counts above 10,000 per cubic millimeter. The lowest was 3,100, and the highest was 46,000.

SEDIMENTATION RATE. The sedimentation rate was determined in 30 patients and was found to be elevated in 24 (80 per cent).

BLOOD CULTURES. Bacteria were cultured from the blood in 32 patients (84 per cent). Of the 6 patients with negative blood cultures, the diagnosis was confirmed at autopsy in 2; 3 had splenomegaly which developed during a febrile illness, and 2 of these had petechiae. The other patient had multiple arterial emboli, fever, malaise, and congestive heart failure.

In 13 (34 per cent of the total group) the organism was identified as *Micrococcus pyogenes* (staphylococcus); 8 of these patients were seen prior to 1956, and 5 after that date. Nine patients (24 per cent) had *Streptococcus viridans* (alpha streptococcus) endocarditis. Two patients had *Streptococcus faecalis* (enterococcus) endocarditis. Five patients had other nonhemolytic streptococcal infections. One each of the following organisms was cultured from the blood of the other 3 patients: *Pseudomonas aeruginosa*, *Aerobacter aerogenes*, and *Brucella suis*.

Bacterial endocarditis in congenital heart disease

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As early as 1844, Paget[1] pointed out the predisposition of the congenitally malformed heart to an infectious process. This observation was later confirmed by Osler,[2] Horder,[3] Abbott,[4] and others.[5] Gelfman and Levine[6] found infectious endocarditis present in 7.7 per cent of 453 autopsied cases of congenital heart disease. Blumenthal and associates[7] noted the incidence of endocarditis to be of 0.50 patients per 1,000 pediatric hospital admissions. This number has remained constant over the 30 years of their study, and has apparently been unaffected by antibiotics. Thus, a patient with congenital heart disease runs a small but definite risk of developing endocarditis. The mortality in undiagnosed cases is still close to 100 per cent. The purpose of this paper is to present a review of all patients with bacterial endocarditis superimposed on congenital heart defects who were seen from May, 1947, to July, 1960, in four hospitals affiliated with Emory University.

Our criteria for including patients in this study were as follows: (1) septicemia in patients with congenital heart disease without other obvious infection; (2) congenital heart disease in patients with negative blood cultures who had a history of prolonged, unexplained fever accompanied by weakness, loss of weight, anemia, splenomegaly, petechiae, or embolic phenomena; and (3) autopsy findings.

Results

Thirty-eight patients were included in the study (Table I). There were 19 males and 19 females. All were less than 41 years of age. The mean age for the group was 15.0 years. There were no differences in mean age between the sexes. The youngest patient was 14 months.

Congenital defects. The congenital defect was diagnosed by physical findings which were confirmed by x-ray examination and fluoroscopy, angiocardiograms, cardiac catheterizations, operation, or autopsies.

Fifteen patients had ventricular septal defects. Coarctation of the aorta was also present in 1, and pulmonic stenosis in 2. In 7 the diagnosis was made on the basis of physical findings, compatible x-ray films, and electrocardiograms. In 4 patients the diagnosis was confirmed by cardiac catheterizations, and in another, by operation. The diagnosis was confirmed in 3 patients at autopsy.

Seven patients had tetralogy of Fallot. In 1 patient the diagnosis was made on

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Embolic complications	Congestive failure	Treatment	Outcome
	No	P, S, N	Recurrence 8 mo.
No	No	P, S, E	Well, 51 mo.
Spleen	No	P, S	Well, 92 mo.
Kidneys	No	P, S, V	Living, subarachnoid hemorrhage, 10 mo.
No	Yes	P, S	Dead, brain abscess
CNS	Yes	P, E, C, T	Dead, CHF
Lung	Yes	P, S, E, T	Well, 77 mo.
No	Yes	P	Well, 146 mo.
No	Yes	P, S	Well, 72 mo.
No	No	P, S	Well, operation at 58 mo.
Kidneys	Yes	P, S	Well, 25 mo.
No	No	P, E	Lost to follow-up
Osler's nodes	No	P, S	Well, 56 mo.
No	No	P	Well, 9 mo.
No	Yes	P, S	Dead, CHF
No	Yes	P, S	Dead, CHF, 6 mo.
CNS	No	P, S	Dead, embolus (?)
Spleen, lung, femoral artery	No	P, S	Well, 1 mo.
No	No	P, S	Lost to follow-up
Spleen	No	Po, T, Ne	Dead, infection
No	Yes	P, S	Well, 52 mo.
CNS, peripheral artery	No	P, S	Well, lost 22 mo.
No	No	P	Lost to follow-up
No	Yes	P	Well, 120 mo.
No	Yes	P, S	Well, 20 mo.
No	Yes	P, S	Well, 66 mo.
CNS	No	P, S	Well, 72 mo.
No	No	P	Well, 149 mo.
No	No	P, S	Dead, CHF
No	No	P, S	Well, 4 mo.
No	No	P, S	Well, 42 mo.
No	No	P, S	Recurrence (1957) 57 mo.
No	No	P	Well, 89 mo.
No	No	P, S	Well, 143 mo
No	None		Dead, ruptured aorta
Kidneys, aorta	Yes	P, S, K, C, F	Well, 8 mo.
Lungs, CNS (?)	No	P	Lost to follow-up
Kidneys	Yes	P	Dead, CHF
Kidneys, CNS, Osler's nodes			

insufficiency. P: Penicillin S, Streptomycin N: Novobiocin E Erythromycin V: Vancomycin C: Chloramphenicol T Tetra

cillin in doses of 20 million units a day for 7 days showed no response in fever, but did respond to kanamycin in doses of 100 to 300 mg. a day for 18 days. Another patient, previously reported on,[8] who had received a total of 270 million units of penicillin over a period of 6 days for staphylococcal endocarditis, and who had shown no improvement, responded to 37 days of therapy with erythromycin and Terramycin. A patient with staphylococcal endocarditis had positive blood cultures after receiving a total of 2.2 billion units of penicillin over a period of 40 days; vancomycin in doses of 2 Gm. daily for 19 days resulted in negative cultures. One patient with endocarditis caused by *Pseudomonas aeruginosa* who was allergic to penicillin was treated with polymyxin, neomycin, and tetracyclines, and expired after 31 days of treatment.

Survival

Eight patients died in the hospital; thi gave a hospital survival rate of 79 per cent Seven of the 8 dead were autopsied. Th

Table I. Data on patients included in the study

Case, Date	Age, Sex	Congenital defects	Duration of symptoms	Organism
1. 1958	8, F	VSD	9 days	Staph. aureus
2. 1954	22, F	VSD	5 wk.	Staph. aureus
3. 1952	17, M	VSD; PS	5 mo.	Staph. albus
4. 1960	15, M	VSD; coarctation of aorta	2 wk.	Staph. aureus
5. 1956	5, M	VSD	3 days	Staph. aureus
6. 1953	5, M	VSD	6 days	Staph. aureus
7. 1953	2, M	VSD	8 days	Staph. aureus
8. 1948	12, M	VSD	5 mo.	Alpha streptococcus
9. 1954	6, F	VSD	6 wk.	Alpha streptococcus
10. 1955	10, F	VSD	2 mo.	Alpha streptococcus
11. 1957	8, M	VSD	8 mo.	Alpha streptococcus
12. 1952	37, F	VSD	3 mo.	Gamma streptococcus
13. 1955	7, M	VSD	5 wk.	Gamma streptococcus
14. 1958	5, F	VSD	6 wk.	Anaerobic strep.
15. 1953	14, M	VSD	4 mo.	Unknown
16. 1955	10, F	Tetralogy of Fallot; ASD	4 mo.	Alpha streptococcus
17. 1955	26, M	Tetralogy of Fallot	7 days	Alpha streptococcus
18. 1960	12, M	Tetralogy of Fallot	18 days	Enterococcus
19. 1950	15, F	Tetralogy of Fallot	8 days	Enterococcus
20. 1954	5, F	Tetralogy of Fallot	4 days	Pseudomonas
21 1955	38, F	Tetralogy of Fallot	3 wk.	Unknown
22. 1952	15, F	Tetralogy of Fallot	3 mo.	Unknown
23. 1950	14 (mo.), F	PDA	3 days	Staph. aureus
24. 1950	9, F	PDA; VSD; coarctation of aorta	3 mo.	Staph. aureus
25. 1958	38, F	PDA	4 mo.	Alpha streptococcus
26. 1954	6, F	PDA	7 mo	Gamma streptococcus
27. 1954	20, F	PDA	5 mo.	Brucella suis
28. 1948	4, F	PDA	1 yr.	Unknown
29. 1947	13, F	PDA	3 wk.	Unknown
30. 1960	40, M	AS	6 wk.	Staph. albus
31. 1956	25, M	AS	8 mo.	Alpha streptococcus
32. 1955	31, M	AS	3 days	Gamma streptococcus
33 1949	9, M	PS	6 mo.	Staph. aureus
34. 1948	7, M	Infundibular pulmonic stenosis	4 mo.	Unknown
35. 1948	37, M	Coarctation of aorta	3 wk.	Staph. aureus
36. 1960	8, M	Truncus arteriosus	6 mo (?)	Aerobacter
37. 1950	23, M	Truncus arteriosus (?)	9 wk.	Alpha streptococcus
38. 1960	8, F	Fibroelastosis; AI	4 mo.	Staph. aureus

VSD: Ventricular septal defect. PS: Valvular pulmonic stenosis. ASD: Atrial septal defect PDA: Patent ductus arteriosus. AI: Aortic cycline Ne: Neomycin. Po: Polymyxin. K: Kanamycin. F: Furadantin. CHF: Congestive heart failure AS: Aortic stenosis.

Treatment

Therapy consisted primarily of penicillin and streptomycin given for several weeks. The dosage varied with the infecting organism. All fatal cases except one were diagnosed prior to death, and therapy was given for a minimum of 4 days. Data on the range and average dose of penicillin and the duration of therapy for the various organisms are given in Table II.

Streptomycin was usually, but not always, given with penicillin. The dosage of streptomycin was 1 to 2 Gm. per day initially, depending on the weight of the patient; the dose was reduced to half the original amount after 1 or 2 weeks. The drug was continued as long as penicillin was given, unless toxic effects developed.

For staphylococcal infections, erythromycin was frequently added to the treatment program in doses of 1 to 3 Gm. daily.

In some instances, other antibiotics were used because penicillin, even in massive doses, did not seem to be effective. One patient with endocarditis caused by *Aerobacter aerogenes* who was given peni-

ductus arteriosus. Four of these underwent operation after successful treatment of endocarditis, and 1 of the 4 developed endocarditis in the immediate postoperative period. This patient was re-explored and an aneurysm of the aorta found. She died the day after operation. The other 2 patients, who were seen in 1947 and 1948, underwent ligation of the ductus to eradicate the infectious foci; both patients made uneventful recoveries. One of these had a ventricular septal defect and a coarctation of the aorta; the latter condition was corrected at a later date.

Four patients with tetralogy of Fallot developed endocarditis after Blalock shunts had been made or similar procedures carried out. The infection began 3 days, 2, 6, and 10 years after the procedure.

Two patients had elective repair of congenital defects 5 and 10 years after their endocarditis. One of these patients had a ventricular septal defect, and the other an infundibular pulmonic stenosis. One patient who underwent an operation for correction of an aorta-pulmonary artery window developed endocarditis 6 months later. Another patient with aortic stenosis underwent surgical repair of a fistula from the aorta to the right ventricle which had resulted from his endocarditis.

Discussion

The predominant infecting organism varies with the series reported. Cutler and co-workers[9] reported alpha streptococcus as the infecting organism in 8 of 16 patients, seen between 1944 and 1956, who had endocarditis superimposed on congenital heart disease. Blumenthal and associates[7] reported 12 patients with alpha streptococcal endocarditis and 8 with staphylococcal endocarditis in a group of 29 patients of pediatric age in whom the diagnosis was made after 1945. They also noted no staphylococcal infections prior to 1940 in a group of 13 patients, 7 of whom had congenital heart disease and the other 6, rheumatic heart disease. The predominant organism in this group was the alpha streptococcus. Nine of the patients in our series, which was collected from 1947 to 1960, had alpha streptococcal infections, and 13 had infections due to staphylococcus. Thus, it seems that staphylococcal infections are becoming a greater problem in congenital heart disease. In our group, at least, this is not related to the increased number of surgical repairs of the congenital defects. Only 2 of our 14 patients who underwent operation had staphylococcal endocarditis, and 1 of these underwent operation after cure of the disease.

Types of congenital defects. The findings of Gelfman and Levine,[6] Blumenthal and associates[7] and our own experiences indicate that endocarditis occurs almost always in the presence of those anomalies with which there are significant pressure gradients across a defect or valve. We have observed the occurrence of vegetations at the site of impact of the jet which streams into the right ventricle and against the septal leaf of the tricuspid valve in ventricular septal defects, at anastomotic sites after Blalock procedures for tetralogy of Fallot, and in the aorta beyond the point of the coarctation.

Diagnosis. Although the diagnosis was made prior to death in all but one of our patients, this had not been the experience of others. Blumenthal and associates[7] reported 7 cases diagnosed at autopsy. Others[10] have reported that as many as 50 per cent of the cases of acute bacterial endocarditis were not diagnosed in life. Thus, emphasis must be directed toward diagnosis. The insidious onset of symptoms, their similarity to those commonly seen in infections of the respiratory tract, and the masking of the underlying disease by embolic complications often obscure the clinical picture. Special attention must be given to those patients with increased pulmonary blood flow who repeatedly are having one "cold" after another. Persistent fever, or fever which recurs after short courses of antibiotics, should compel one to consider the diagnosis of endocarditis. Loss of weight, easy fatigability, and night sweats in patients with congenital heart disease may be the only symptoms of endocardial infections for several months. Meningitis, pyelonephritis, brain abscesses, strokes, hematuria, pulmonary emboli, all common results of embolic complications, may be the presenting symptoms. On occasion, progressive heart failure may be

Table II. Data on penicillin therapy

Infecting organism	Penicillin (million units) Daily dose		Duration (days)	
	Average	Range	Average	Range
Staphylococcus	30.6	0.4–125	20.7	4–60
Alpha streptococcus	9.5	1–50	19.7	4–35
Nonhemolytic streptococcus	12.1	5–24	23.8	17–42
Enterococcus (2 cases)	9.5	2–20	21.5	20–24
Other (3 cases)	17.1	0–20	19.6	7–31
Unknown	19.8	4–24	29.6	19–48

one patient not autopsied had been seen in 1948. She had undergone ligation of a patent ductus because of recurrent endocarditis. Fever and a continuous murmur developed postoperatively. She was treated with 5 million units of penicillin daily for 25 days; re-exploration while she was still under treatment revealed an unresectable mycotic aneurysm. She died of congestive heart failure on the day after the operation. Three autopsied patients had died of congestive heart failure. Two of these had emboli to the central nervous system. One patient who died of uncontrolled infection after a Blalock procedure had not been given penicillin because of allergy. Autopsy showed that colonies of bacteria were present at the site of anastomosis. Two patients died of embolic complications: one of ruptured brain abscess, and the other after an embolus to the femoral artery. One patient, whose condition was undiagnosed in life, died of a ruptured mycotic aneurysm of the aorta at the site of a coarctation.

Only 1 patient died after treatment for endocarditis. She died of congestive heart failure within the first year after discharge.

Fifteen patients were living and well from 1 month to 149 months after discharge. Seven patients reported that they were well, but that they tired easily. Two were known to be taking digitalis. Two patients were well after treatment for recurrent endocarditis a year later. Subsequently, 6 had successful surgical repair of their congenital defects.

In 1 patient with congenital aortic stenosis a fistula developed between the aortic cusp and the right ventricle. This was surgically corrected at another institution.

Four patients were lost to follow-up.

Factors which affect prognosis

Because of the small number of patients involved, statistically significant differences are not possible to determine. However, certain trends affecting prognosis seem to be evident.

Congestive heart failure. During hospitalization, 4 of the 14 patients with heart failure died (29 per cent mortality). There was a 17 per cent mortality among the other 24 patients without heart failure.

Emboli. Five (29 per cent) of the 17 patients with embolic phenomena died during hospitalization. Two of these had congestive heart failure. Death occurred in 3 of the 28 patients without emboli (11 per cent mortality).

Organism. Four of the 13 patients with staphylococcal endocarditis died (31 per cent). The results were graver than in those infected with other organisms; in the latter group, only 16 per cent died.

Duration of symptoms. Six of the 14 patients who had symptoms less than 4 weeks died (43 per cent); this is in contrast to 2 deaths in 24 patients who had symptoms longer than 4 weeks (8 per cent).

Relation of endocarditis to operation

Fourteen patients underwent some type of corrective surgical procedure. Six patients submitted to ligation of a patent

other infections, is strongly recommended.

OTHER STREPTOCOCCI. For other streptococci, 12 million units of penicillin daily and streptomycin should be given for 3 to 4 weeks.

UNKNOWN ORGANISMS. In the case of unknown organisms, 8 to 12 million units of penicillin daily and a doubling or redoubling of the dose, depending upon the clinical response, is suggested. Streptomycin is indicated also. Treatment should continue 4 weeks.

Complications of therapy. Allergic reactions to penicillin develop in a small percentage of patients and are most often manifested by a maculopapular pruritic rash. The use of antihistamines and corticosteroids should be tried before the administration of the antibiotic is stopped.

The dangers of involvement of the eighth nerve which result from the use of streptomycin and dihydro-streptomycin are well known. These drugs should be discontinued at the first appearance of toxic symptoms.

When massive doses of potassium penicillin are administered in small infants, the development of hyperkalemia becomes a possibility. This is particularly important if there is evidence of renal damage with inadequate output of urine. A similar situation exists in the case of the sodium salt of penicillin, massive doses of which may aggravate congestive heart failure. One brand of crystalline sodium penicillin is known to contain 40 mg. of sodium per million units of penicillin. Potassium penicillin contains 65 mg. of potassium per million units.

DRUG FEVER. Occasionally, after several weeks of antibiotic treatment, patients may again develop fever. A problem arises in differentiating between an exacerbation of the infection and the development of "drug fever." In these instances, we suggest that all antibiotics be stopped for 24 to 48 hours, and that the blood cultures then be repeated. If the fever subsides and the cultures remain sterile, no further therapy is indicated.

Despite an otherwise satisfactory clinical response of the patient, fever may return in the first week or 10 days of therapy. In such cases, antihistamines are added to the infusion, blood for culturing is drawn, and the fever observed for 24 to 48 hours. If there is no response during this period, the dose of antibiotic is doubled, and a second period of observation is carried out. With no response and with negative cultures, a decision is then made on clinical grounds whether to change antibiotics or to continue with the present treatment; with no response and with positive cultures, the sensitivities are repeated and appropriate changes in therapy are made.

Summary

A study was made of 38 patients who developed bacterial endocarditis as a complication of congenital heart disease; in these patients, who were seen from 1947 through 1960, the staphylococcus was the infecting organism found most frequently.

All patients presented with fever, and 79 per cent developed splenomegaly at sometime during the illness.

Embolic manifestations often masked the underlying disease.

Congenital anomalies, which cause significant pressure gradients and jet effects across defects or valves, predispose to endocarditis.

Penicillin in adequate doses, together with streptomycin, is the mainstay of treatment and should be administered from 3 to 4 weeks. On occasion, other antibiotics are added.

Seventy-nine per cent of the patients survived hospitalization Only 1 patient died subsequent to discharge. With the exception of 4 patients who were lost to follow-up, the others are alive, 1 month to 12 years after hospitalization.

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the presenting condition. Blood for culturing should be drawn from any patient with congenital heart disease who presents in this fashion.

Most patients will eventually have some additional physical manifestations which assist in the diagnosis. Half of the patients reported by Blumenthal and associates[7] had splenomegaly, as did 79 per cent of our group. Other well-known manifestations of bacterial endocarditis, such as petechiae, Osler's nodes, and Janeway spots, are helpful but are not frequently present. Microscopic hematuria was found in half of the cases reported by Blumenthal, and in only 13 per cent of ours. Clubbing is not often seen, except with cyanotic congenital defects, and is of little help.

Duration of symptoms. The duration of symptoms appears to be related to the virulence of the organism. We disagree with Blumenthal's findings that the duration of symptoms had no demonstrable effect upon outcome. Our study showed a higher mortality in those patients who had symptoms less than 4 weeks. It is in this group with the more virulent infections and the earlier serious complications that recognition is easier, but mortality is high, nevertheless.

Treatment. The principle of treatment is to administer enough of a bactericidal agent over a sufficient period of time to permit penetration of the vegetations and destruction of the infecting organisms. Penicillin penetrates fibrin clots[11] in direct proportion to its concentration in the serum and duration of contact with the clot.[12] The synergistic action of penicillin and streptomycin has been shown.[13] The amount of antibiotic and the length of time of treatment needed for any individual patient has been arrived at through clinical experience and varies with the virulence and resistance of the particular organism. In vitro sensitivities serve as a crude guide to therapy, but may be misleading both from the standpoint of selection of the antibiotic and the resistance of the organism. For this reason, we prefer to use a serum tube-dilution method. If the patient's serum, diluted four times, is bactericidal, the dosage of the antibiotic is considered to be adequate for treatment.

Penicillin and streptomycin are the antibiotics of choice and are effective in most cases. Other bactericidal drugs, such as vancomycin, erythromycin, polymyxin, neomycin, chloramphenicol, and bacitracin, have been used when necessary. We do not believe that bacteriostatic drugs, such as the tetracyclines, should be used as initial treatment of endocarditis, regardless of sensitivity studies. The penicillin may be administered by continuous intravenous clysis through a polyethylene catheter or by intramuscular injection. The site should be changed at the first sign of phlebitis, usually about every 3 to 5 days. Small scalp vein needles have been used in superficial veins of the arm on many occasions and provide a relatively atraumatic, easily changed avenue for 24-hour infusions. We do not use oral antibiotics because of the variability of intestinal absorption and the possibility of inadequate levels of blood.

The daily dose of penicillin is determined by the bacteriologic findings. Until the organism is identified, we recommend starting with 8 to 12 million units of penicillin daily. Somewhat smaller doses may be used in infants, but, in general, almost the adult dose is given. This is usually combined with streptomycin in doses of 50 mg. per kilogram for 1 week and then reduced to 25 mg. per kilogram after that. If there is no response in the patient's clinical condition within 24 to 48 hours, the dosage of penicillin should be doubled. Once the organism is known the following schedule is recommended.

STAPHYLOCOCCUS. For staphylococcus, the daily requirement of penicillin should be between 40 and 50 million units, continued for 4 weeks. Streptomycin in the dosages stated above is also indicated. The addition of erythromycin, tetracycline, chloramphenicol, novobiocin, bacitracin, or kanamycin is often essential in the case of particularly resistant strains.

ALPHA STREPTOCOCCUS. For this organism, 6 to 12 million units of penicillin daily is the requirement, and streptomycin should be given for 3 weeks.

ENTEROCOCCUS. This more resistant organism usually requires 20 million units of penicillin daily for a period of 28 days. Streptomycin in doses of 50 mg. per kilogram, which is somewhat higher than for

Experimental and laboratory reports

Hemodynamics during mechanical ventilation

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Hemodynamic changes under conditions in which human subjects or animals breathe against a continuous positive or negative pressure applied in the trachea have been the object of several papers.[1-9] Hemodynamic studies in human beings under mechanical ventilation by cycling devices, intermittent positive pressure breathing (IPPB), or positive-negative pressure breathing (PNPB) are scanty.[10-14]

This study was set up in order to observe the behavior of cardiac output, so-called "central blood volume," and vascular pressures in patients with neurogenic chronic respiratory paralysis, and chronic pulmonary emphysema with or without decompensated "cor pulmonale," who were passively ventilated by either body-respirators (Drinker type) or intermittent positive pressure (IPP) apparatus.

Material and methods

A group of young patients (8 patients, one of whom was studied twice) with chronic respiratory paralysis (CRP) due to poliomyelitis or other neurological conditions was studied while they were breathing spontaneously and after at least 1 hour under mechanical ventilation—8 of them with body-respirators, 1 with an IPP machine (Bang apparatus). Five patients with chronic pulmonary emphysema (CPE) were studied in exactly the same way; in one of them who had previously undergone tracheotomy, an Engström (constant volume) respirator was used. Another group of 4 patients with chronic pulmonary emphysema and decompensated "cor pulmonale" was also studied, one of them with an Engström respirator. One patient with myasthenia gravis, who was completely paralyzed, was studied while he was under artificial ventilation with the iron lung and thereafter with an Engström respirator. All these patients suffered severe respiratory insufficiency and were either chronic respirator cases or were subjected periodically to artificial ventilation. In all cases, complete adaptation of the patient to the respirator was obtained before the studies were begun. We always tried to set the machine so as to give a ventilation similar to that obtained during spontaneous breathing. In some cases, adaptation was obtained only at the cost of some hyperventilation, and although that may have been undesirable, no other choice seemed available, except heavy sedation or muscle relaxants, which we did not care to use.

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as cardiac output; in fact, "central" blood volume increased in 2 cases (Fig. 1). Blood volume was not appreciably modified except in Case 5, in which it fell; this was a child with anemia.

Pulmonary vascular pressures were measured in 3 patients. Mean pulmonary arterial transmural pressure decreased in all. In 2 of them (Cases 7 and 8), because of the concomitant but very small decrease in cardiac output, the change in total pulmonary resistance was similar to the modification in vascular pressure. In the other one, cardiac output changed in the same direction and amount so that resistance stayed the same. In one of these

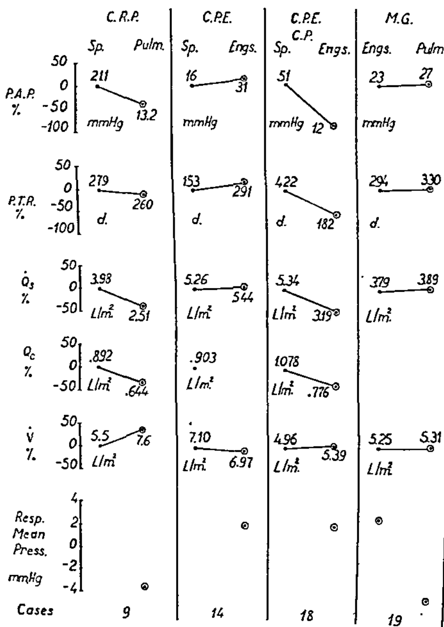


Fig. 2. Changes in the hemodynamic and respiratory variables in several patients under mechanical ventilation. Zero per cent is the figure which represents spontaneous breathing. The other figures represent absolute values obtained. The abbreviations correspond to those used in Table I. *P.A.P.*: Pulmonary arterial pressure. *P.T.R.*: Total pulmonary resistance.

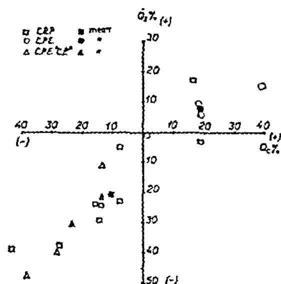


Fig. 1 Effects of mechanical ventilation upon cardiac index ($\dot{Q}_i$) and "central" blood volume (Q_c). *C.R.P.*: Chronic respiratory paralysis. *C.P.E.*: Chronic pulmonary emphysema. *C.R.P. "C.P."*: Chronic pulmonary emphysema and "cor pulmonale." The mean values are indicated by the solid black symbols.

An indwelling Cournand needle was introduced into the brachial artery of all patients; and a radiopaque catheter was advanced into a brachial vein, which in some was left at the entrance of the right auricle, but which in others was advanced into the trunk of the pulmonary artery.* Expired gases were collected during 3 minutes into a Douglas bag through a three-way, low-resistance valve, fitted either to the mouth or to the tracheal cannula. In patients who were under IPP the collection of gas was carried out through the expiratory tube of the Engström respirator or of the Bang apparatus. At the end of the first minute of gas collection, blue dye T-1824 was injected through the venous catheter in less than 1 second. After 5 to 7 seconds, arterial blood was collected every 2 seconds. In some cases a sample was taken simultaneously from the pulmonary and brachial arteries in order to obtain the A-V difference and compute the cardiac output by the Fick method. Vascular pressures were measured with Statham P23DD strain gauges connected to Sanborn Poly-Viso direct-writing recorders; records were taken immediately before and after injection of the dye. Intrathoracic pressures were estimated by measuring pressures developed in a multiholed polyethylene tube covered by a latex balloon and placed in the esophagus. Pressure in the IPP apparatus was measured by placing a polyethylene catheter in a side tube directly connected to the tracheal cannula. Vascular pressures were all transmural. Vascular resistance was estimated by using mean absolute pressures. Cardiac output, mean circulation time, and "central" blood volume were measured by the standard technique already described.[14]

A glass electrode and Beckman pH meter were used for determination of blood pH. Blood gases were measured by the Van Slyke and Neill manometric technique. Expired gas was analyzed in a Scholander micro gas analyzer, and arterial pCO_2 was estimated by the Henderson-Hasselbalch equation.

*Changes in mean circulation times and "central" blood volumes due to different positions of the catheter may occur, but since the comparisons are made only between different conditions in the same patient, that does not affect the results.

Results

In chronic respiratory paralysis (Table I) the volume of ventilation was increased in all cases except one (Case 5); the mean was 25.1 per cent higher than during spontaneous breathing. Respiratory rate showed small changes around a mean of −1.3 per cent. In 4 of the 5 cases in which they were measured, pH and arterial pCO_2 changed significantly in the direction of a moderate, acute respiratory alkalosis; in the other they remained the same in spite of increase in total ventilation.

Arterial oxygen saturation increased in Case 5 because of the use of oxygen as source of energy for the positive pressure respirator. The respiratory quotient was not modified in 3 of the 4 cases in which it was measured; its increase in Case 8 in spite of the constancy of pH and pCO_2 shows that the patient might not have been in a steady state.

The cardiac index decreased in all cases except one (Case 6); the mean total change was −20.5 per cent. As in the next group, the increase in mean circulation time tended to compensate that change in relation to "central" blood volume, so that this last parameter did not show such a fall

Δ (%)	M.C.T	Δ (%)	$\dot{Q}_c$ (L./M.²)	Δ (%)	Q_c (L./M.²)	Δ (%)	SaO_2 (%)	$CaCO_2$ (vol.%)	$PaCO_2$ (mm. Hg)	R	pH	Hct. (%)
−23.4	14 7	+20 3	2 980	−4 5	1 370	−7.4	98.4	55 1	—	—	—	—
	17 8		2 850		1 270		—	—	—	—	—	—
−29.5	13.3	+20.0	1.985	−2 0	1.260	−14 8	92 0	46.4	—	—	—	40.0
	16 0		1.940		1.075		93 0	45.5	—	—	—	40 0
−24 3	15 8	+11.0	2 920	+5 0	0 697	−15 7	94.8	47.6	—	—	—	42 0
	17 5		3 080		0 587		98.6	45 1	—	—	—	42 0
−39 0	14 0	−9 5	2 170	−5 0	1 085	−44 4	90 9	45 5	47	—	7 31	46 5
	12 7		2 062		0 604		89 1	37 4	31	—	7 43	46 5
−24 5	12 7	+13 8	2 740	−29 2	0 738	−14 4	91 8	46 9	—	—	—	28 5
	14 5		1.940		0 632		100+0.6	46.3	—	—	—	29 0
+17.4	14 1	0	2 420	−7 0	0 955	+15.7	91.8	44 9	39	0 770	7 39	38 0
	14 1		2.250		1.105		94.7	38 5	27	0 80	7 50	38.0
−2 9	21 2	+21 7	—	—	0 917	+18 5	94 9	46 2	38	0 833	7 43	46 0
	25 8		3 060		1 085		93 9	39 0	26	0 820	7 52	46 0
−5 0	9 7	−2 0	2 115	—	0 718	−8 0	93 8	46.5	40	0 740	7 39	38.0
	9 5		—		0 660		93 3	43.7	38	0 950	7 39	37 5
−37 1	13 4	+14 0	2 660	+2 0	0 892	−27 8	98 4	51 0	46	0 747	7 37	42.0
	15 3		2 710		0 644		93 1	43 7	29	0 862	7 52	41 0
−20 5		+10 9		−6 8		−11 9						

motor B Bang respirator. $\dot{Q}_c$: Cardiac index M.C T.: Mean circulation time Q_v: Blood volume. Q_c: "Central" blood volume. quotient Hct: Hematocrit. C.R.P : Chronic respiratory poliomyelitis. C P.. Cerebral paralysis. T.P.: Traumatic paraplegia.

and without "cor pulmonale" and should be analyzed separately. In the group without heart enlargement, as determined by x-ray film, mean cardiac output increased 6 5 per cent; the change was not considered to be significant. Since mean circulation time increased also, "central" blood volume was augmented 19.6 per cent in the whole group. In the group with "cor pulmonale," cardiac output decreased in all cases; the mean fall was 20.3 per cent. Mean circulation time tended to increase and "central" blood volume decreased in all of them, although proportionately less than blood flow (Fig. 1).

Pulmonary vascular pressures were obtained in 1 patient of each group. In the patient without "cor pulmonale" (Case 14, Table IV) the pulmonary arterial mean transmural pressure increased, with a similar increase in total pulmonary resistance. In the other patient with "cor pulmonale" (Case 18), pulmonary arterial mean pressure and total pulmonary re-

Table I. Chronic respiratory paralysis

Case	Diagnosis	Name	Age	B.S.		$\dot{V}$ (L./M.²)	Δ (%)	F	Δ (%)	Respirator mean pressure (mm. Hg)	$\dot{Q}$ (L./M.²)
1.	C.R.P.	P.C.	26	1 535	1	5 91	+2.4	30	−13.0	—	5.43
					2	6.05		26		−4.9 P	4.16
2.	C.R.P.	J.T.	21	1 375	1	3.10	+27.7	19	−10.0	—	5 76
					2	3 96		17		−3.4 P	4.05
3.	T.P.	S.M.	19	1 68	1	4 48	+22 5	17	+9.0	—	2 65
					2	4 78		18		−2 9 P	2 01
4.	C.R.P.	A.G.	20	1 78	1	5 45	+6 7	22	+5.0	—	4 67
					2	6 67		21		−3.7 P	2 85
5.	C.P.	E.L.	8	0 77	1	5 16	−29.6	27	−11.0	—	3 46
					2	3 63		24		+2 0 B	2 61
6.	C R.P.	T.B.	14	1.28	1	5 74	+44 3	14	+14.0	—	4 00
					2	8 28		16		−4 6 P	4.70
7.	T.P.	S.M.	20	1 68	1	3 90	+52 5	16	−6.0	—	2 59
					2	5 95		15		−2 8 P	2 52
8.	C R.P.	J.C.T.	12	1.02	1	4.45	+40.4	18	0	—	4.42
					2	6.25		18		−3 1 P	4 19
9.	C.R.P.	E.T.	25	1.52	1	5 53	+37.5	21	0	—	3.98
					2	7 60		21		−3.5 P	2.51
Mean							+25.1		−1.3		

Abbreviations—B S · Body surface area. 1: Spontaneous breathing. 2: Artificial respiration. $\dot{V}$: Ventilation. F: Respiratory rate. P: Pul-
SaO_2: Arterial oxygen saturation. $CaCO_2$: Total arterial carbon dioxide. $PaCO_2$: Arterial carbon dioxide tension. R: Respiratory

patients (Case 9), "central" blood volume changed in the same direction with cardiac output and pulmonary arterial pressure; in the other (Case 7), "central" blood volume increased in the face of a decrease in pulmonary arterial pressure and resistance (Fig. 2).

In chronic pulmonary emphysema (Table II), ventilation and the rate of the spontaneous breathing period were maintained during artificial respiration in the whole group, except in Case 13, in which rate was decreased, and Case 12, in which ventilation had to be increased in order to obtain adaptation to the respirator.

In all cases, arterial oxygen saturation increased and respiratory acidosis was totally or partially corrected, as measured by changes in arterial pCO_2 and pH. In the 5 cases in which pH was not measured, arterial carbon dioxide decreased, between 2.1 and 7.1 volumes per cent, showing the same trend. Hemodynamic variables showed different trends in patients with

Δ (%)	M.C.T.	Δ (%)	Q. (L./M.²)	Δ (%)	Q. (L./M.²)	Δ (%)	SaO_2 (%)	$CaCO_2$ (vol. %)	$PaCO_2$ (mm. Hg)	pH	R	Hct. (%)
A. Chronic Pulmonary Emphysema												
+9 0	16 3	+9 8	2.855	+2 5	0 672	+18 7	86 6	49.7	—	—	—	44 9
	17.9		2 915		0 798		89 9	42 6	—	—	—	—
−0 9	16.3	+1 5	2 720	−4 5	1 000	+1 0	89 1	50 1	—	—	—	41 8
	16 5		2 600		1 010		91 0	48 0	—	—	—	41 8
+15 0	15 5	+20 5	3 250	−5 3	0 616	+39 6	94 8	50 8	—	—	—	41 5
	18 7		3 080		0 860		96 0	47.3	—	—	—	41 0
+5 7	14.7	+13 0	2 165	−6 8	0 605	+19 2	91 0	48 6	—	—	—	50 0
	16 5		2 020		0 721		96.3	45 2	—	—	—	50 0
+3 5	17 7	—	2 465	—	0 903	—	74.8	56 9	46	7 40	826	36.0
	—		—		—		77.9	54 1	41	7 43	821	36.0
+6 5		+11 2		−4.7		+19 6						
B. Chronic Pulmonary Emphysema and "Cor Pulmonale"												
−22 5	18.2	+6	3.485	+19 3	1 242	−13 7	83 4	51 0	—	—	—	61 4
	19.4		4 160		1 072		91 4	47 9	—	—	—	60 6
−47 8	23 8	+12 5	4 455	—	3 560	−39.1	78 0	62 5	57	7.34	—	58 0
	26.8		—		2 170		81 8	60 7	50	7 39	—	58 0
−10 8	19 3	−4 0	3 200	−16 8	0 928	−13 5	89.9	57.4	46	7 40	—	55 5
	18 5		2 665		0 802		94.6	54 3	41	7 43	—	55 0
−40 0	12.1	+20 7	2 720	−8 3	1 078	−28 0	77 6	62 3	51	7 41	800	47 0
	14 6		2.495		0 776		81 8	58 4	44	7.44	.810	41 0
−30 3		+8.8		−1 93		−23.6						

1. When positive pressure is applied, intrathoracic pressure is increased in variable amounts. When normal lungs are considered, the changes in thoracic pressure are about 50 per cent of applied pressure, depending on the elastic characteristics of the interposed lungs.[5,7,8]

2. Simultaneous increase in peripheral venous pressure[1,2] and right auricular and pulmonary arterial pressures has been described.[7,9,16] In animals with the chest open, a delayed fall in pulmonary vein wedge and left auricular pressures, confronted with increased pulmonary arterial

Table II. Chronic pulmonary emphysema

Case	Diagnosis	Name	Age	B.S.		$\dot{V}$ (L./M.²)	Δ (%)	F	Δ (%)	Respirator mean pressure (mm. Hg)	$\dot{Q}_s$ (L./M.²)
A. Chronic Pulmonary Emphysema											
10	C.P.E.	C.C.	60	1.638	1	6.29	+4.4	25	+12.0	—	2.47
					2	6.58		28		−8.2 P	2.69
11	C.P.E.	C.J.C.	62	1.64	1	6.70	−9.5	20	+10.0	—	3.70
					2	6.06		22		−5.6 P	3.66
12	C.P.E.	P.G.	63	1.63	1	4.76	+35.0	16	0	—	2.40
					2	6.42		16		−4.9 P	2.77
13.	C.P.E.	P.B.	61	1.985	1	7.62	−9.3	30	−26.7	—	2.47
					2	6.91		22		−8.6 P	2.62
14.	C.P.E.	A.B.	62	1.57	1	7.10	−1.8	29	−6.9	—	5.26
					2	6.97		27		+2.1 E	5.44
Mean							+3.8		−2.3		
B. Chronic Pulmonary Emphysema and "Cor Pulmonale"											
15.	C.P.E. C.P.	J.M.	60	1.67	1	4.40	−6.1	18	−11.1	—	4.10
					2	4.13		16		−4.9 P	3.22
16.	C.P.E. C.P.	C.C.	33	1.55	1	4.19	+5.8	16	−0.6	—	9.10
					2	4.45		15		−7.3 P	4.85
17.	C.P.E. C.P.	R.E.	58	1.67	1	5.50	+4.0	20	−10.0	—	2.88
					2	5.72		18		−5.6 P	2.60
18.	C.P.E. C.P.	H.V.P.	58	1.79	1	4.96	+8.7	17	0	—	5.34
					2	5.39		17		+2.4 E	3.19
Mean							+2.5		−5.4		

Abbreviations correspond to those used in Table I. E: Engström respirator.

sistance decreased markedly, together with a fall in cardiac output and "central" blood volume (Fig. 2).

Discussion

On the basis of work dedicated to the study of hemodynamics during continuous positive pressure* breathing in animals and human beings, several facts seem well established:

*Reference is made to positive pressure breathing because it is the method we used, either directly (tracheal application: Engström or Bang machines) or indirectly (negative pressure around the body: iron lung).

$\dot{Q}_s$ (L./M.²)	Δ (%)	Q_s (L./M.²)	Q_c (L./M.²)	SaO_2 (%)	$CaCO_2$ (vol. %)	$PaCO_2$ (mm. Hg)	R	pH	Hematocrit (%)
3 79	+2 5	—	—	92 6	36 3	29	.797	7.41	38
3 89		2 83	1 015	91.9	35.4	28	.705	7.41	38

whereas it decreases with CPP. With IPP, an inspiratory increase in systemic arterial pressure is observed as a consequence of the supporting effect on the thoracic aorta by the increase in intrathoracic pressure.

In our cases, we were interested in observing the situation in patients subjected to commonly employed respirator devices. Although in all cases we applied either positive tracheal pressure or negative perithoracic pressure, this was done intermittently, thus making these studies different from those done with continuous positive or negative pressure.

Apart from the technical difficulties involved in taking samples of blood from the patients placed in body-respirators, the most important problem was to obtain complete relaxation and adaptation of the patients to the machines used, with ventilation and breathing rate similar to that found in spontaneous breathing. Adaptation was not difficult since the patients were accustomed to mechanical ventilation. In a broad way, this could be judged by the lack of demonstrable spontaneous changes in the esophageal pressure curves. The existence of some muscular cooperation with inspiratory action of the respirators, when perfectly timed, cannot be estimated. However, in these severely incapacitated patients, it would have produced some dyspnea and activity of the accessory muscles of breathing, but we did not observe this. The determinations were carried out between 60 and 90 minutes after artificial ventilation was started. Results with tracheal positive pressure devices and negative pressure body-respirators are grouped together, since no difference in effect upon the measured variables was observed in one patient who was studied with both types of machines (Case 19, Table III).

The fall in blood flow found by Kilburn and associates[5] in normal subjects under continuous pressure breathing was obliterated by hyperventilation with arterial pCO_2 kept constant by inhalations of carbon dioxide. We cannot compare the effects of hyperventilation in our study with those observed by Kilburn, because we obtained it either by raising the mean tracheal and thoracic pressures (positive pressure devices) or increasing the negative pressure given by the body-respirator, which has the same meaning. In Kilburn's study,[5] hyperventilation was spontaneous and, therefore, produced by an increase in negative thoracic pressure; thus, venous return may be increased by inducing higher blood flow.

In our cases, the respirator mean pressures are not similar because we tried to keep ventilation as near as possible to the previous spontaneous level. This demanded a different respirator setup in individual patients.

In the group of patients with chronic pulmonary emphysema, one of the readily visible effects of artificial ventilation was the drop in arterial pCO_2 or total carbon dioxide in the face of minor changes in ventilation or breathing rate. The effect may be attributed to better intrapulmonary distribution of inspired air (which has been denied by Torres and associates[18]) or a fall in the production of carbon dioxide, or both. A decrease in the output of carbon dioxide might be produced by the substitution of the respirator for the action of the respiratory muscles; the disappearance of their contribution to the production

Table III

Case	*Diagnosis*	*Name*	*Age*	*B.S*	$\dot{V}$ (*L./M.*²)	Δ (%)	*F*	Δ (%)	*Respirator mean pressure* (*mm. Hg*)
19.	M G.	A.V.	43	1 65	1:5.25 2:5 31	+1 0	20 18	−10 0	(E)+ 3 0 (P) − 3 7

Abbreviations correspond to those used in Tables I and II

and pulmonary arterial wedge pressures, has been described. These events localize the site of vascular obstruction, but this dissociation is absent when the chest is closed.[16]

Transmural vascular pressures are generally not modified because the increase in thoracic pressure accounts for the change produced[10,16] when the chest is closed.

3. *In normal human beings (with IPP)* the fall in right ventricular end-diastolic pressure shows a good correlation with the decrease in blood flow and with mask mean pressure.[10,11] Systemic arterial pressure also falls in relationship to the pressure applied.[2,17] The fall in cardiac output seems to depend on decreased venous return, which is interfered with by the positive thoracic pressure. The diameter of the heart or pulmonary veins and vena cava is decreased, as shown by radiologic estimation [8,9] In human beings under continuous positive pressure, voluntary hyperventilation, with conservation of arterial pCO_2, at a constant level, is capable of impeding the reduction in cardiac output,[8] most likely via the re-establishment of normal venous return.

Preservation of abdominal muscle tone seems to be a positive factor in the homeostatic response to positive pressure breathing,[3] whereas a decrease in blood volume, deep anesthesia, or ganglionic blocking are negatively correlated with the maintenance of cardiac output or arterial pressure.[3,9,12] External counterpressure diminishes the changes in vascular pressures and impedes overdistention of the lungs.[6]

4. Blood is displaced from the lungs to the periphery when positive pressure is applied.[1,2,3]

Comparison between the effects of continuous positive pressure (CPP) and those of intermittent positive pressure (IPP) is somewhat confusing because there is no experience with both methods applied to the same subject. The hemodynamic effect is thought to be related to the increase in mean intrathoracic pressure, and with CPP this is always higher than with IPP. With CPP the effect will also *depend upon whether the chest is open or* closed; in the former case the hemodynamic changes will be related mechanically to alveolar pressure affecting only the pulmonary capillaries, whereas in the latter case it is the peripheral venous return that is directly affected by the increase in intrathoracic pressure.

Cardiac output is decreased by CPP, and less so by IPP. Central blood volume is also decreased by CPP, whereas it is unchanged or very slightly decreased or increased with IPP. Mean absolute pulmonary arterial pressure will rise with CPP and IPP, but net or transmural pressure will diminish if cardiac output has fallen, because, when the chest is closed, vascular resistance is not expected to change, except secondary to the change in pulmonary arterial pressure. When the chest is open, pulmonary arterial pressure rises under CPP. End-diastolic right ventricular pressure is increased with CPP and IPP when one considers absolute values, but transmural pressures show either no change or a slight fall if venous return has been impaired. Mean right auricular pressure shows the same trend as right ventricular pressure. Peripheral venous pressure increases with both CPP and IPP, depending upon the rise in intrathoracic pressure. Systemic arterial pressure shows a very slight change with IPP,

Δ (%)	$\dot{Q}_e$ (L./M.²)	Δ (%)	Q_e (L./M.²)	Δ (%)	Respirator mean pressure (mm. Hg)	Esophageal pressure (mm. Hg)	
							Mean
−62.3	2.59	−3.0	0.917	+18.5	—	(I) − 6.2 (E) 0	−2.5
	2.52		1.085		−2.1	(I) − 5.3 (E) + 0.9	−1.2
−15.1	4.42	−5.2	0.718	−8.0	—	(I) − 1.9 (E) 0	−0.8
	4.19		0.660		−2.6	(I) − 3.2 (E) + 1.8	−0.6
−7.0	3.98	−37.1	0.892	−27.8	—	(I) − 4.9 (E) + 1.9	−0.4
	2.51		0.644		−3.5	(I) − 4.5 (E) + 1.9	−0.8
+90.0	5.26	+3.5	0.903	—	—	(I) − 7.5 (E) + 4.7	−1.0
	5.44		—		+2.1	(I) + 2.5 (E) 0	+0.8
−56.8	5.34	−40.2	1.078	−28.0	—	(I) − 8.8 (E) + 4.7	−1.1
	3.19		0.776		+2.4	(I) + 3.4 (E) 0	+0.8
+11.2	3.79	+2.5	—	—	+3.0	(I) + 2.2 (E) 0	+0.4
	3.89		1.015		−3.7	(I) − 5.4 (E) + 3.4	−0.7

showed minor changes which might be due to an adequate response of the homeostatic mechanisms, such as increased peripheral muscle tone, vasoconstriction, etc. Delay in mean circulation time, a common characteristic in all patients subjected to mechanical ventilation,[14] together with the described changes in blood flow, induced the increase seen in "central" blood volume. This might also be instru-

Table IV

Case	Diagnosis	Situation		Pulmonary arterial pressure (mm. Hg) (Transmural) Systolic	Diastolic	Mean	Δ (%)	T.P.R. (dynes sec. cm.⁻⁵)
7.	T.P.	Sp.	(I)	26.6	4.6	7.9	−67.1	191
			(E)	21.9	1.3			
		P.	(I)	14.6	0	2.6		72
			(E)	11.5	0			
8.	C.R.P.	Sp.	(I)	16.6	6.1	11.1	−15.5	212
			(E)	20.4	6.8			
		P.	(I)	16.4	4.6	9.4		180
			(E)	17.2	9.1			
9.	C.R.P.	Sp.	(I)	31.1	14.1	21.1	−37.4	279
			(E)	34.9	14.9			
		P.	(I)	11.4	5.5	13.2		260
			(E)	23.1	9.5			
14.	C.P.E.	Sp.	(I)	34.2	7.5	15.8	+96.8	153
			(E)	37.3	6.5			
		Eng.	(I)	50.4	25.2	31.1		291
			(E)	46.6	23.3			
18.	C.P.E.	Sp.	(I)	75.4	27.3	51.3	−76.6	422
			(E)	106.3	36.0			
	C.P.	Eng.	(I)	26.8	4.0	12.0		182
			(E)	25.7	7.1			
19.	M.G.	Eng.	(I)	31.9	20.6	23.0	+11.7	294
			(E)	26.9	15.7			
		P.	(I)	31.2	24.8	27.0		330
			(E)	26.9	20.5			

Abbreviations correspond to those used in previous tables. Sp: Spontaneous breathing. I: Inspiration. E: Expiration.

of carbon dioxide by the body might be important in patients with pulmonary emphysema. *In regard to 2 patients in* whom arterial pCO_2 decreased and ventilation changed slightly, the production of carbon dioxide remained the same in one (Case 14) and decreased 15.5 per cent in the other (Case 18).

In the group of patients without clinical signs of "cor pulmonale," blood flow

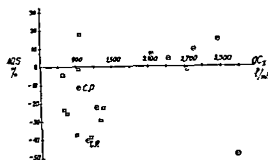


Fig. 3. Changes in cardiac index (ΔQS) under mechanical ventilation as related to initial "central" blood volume (QC_1).

the total change, or a concomitant similar modification may be assumed in the vascular lumen.

The presence of a normal "central" blood volume has been established as one of the means by which cardiac output may be maintained for some time in spite of decreased venous return.[23] Berneus and associates[14] showed in 3 cases of acute poliomyelitis that the head-low position impeded the fall in cardiac output which is associated with positive pressure breathing. They believe that it is probably due to the increase in "central" blood volume which that position must have produced. It is interesting to note that in 2 of their cases the cardiac output did not fall 20 minutes after the horizontal position was resumed, which leaves room for further investigation of this point. No relationship was apparent in our cases (Fig. 3) between the fall in cardiac output and the initial volume of "central" blood.

The fact that the decrease in venous return in cases of chronic respiratory paralysis and "cor pulmonale" is not compensated may point to impaired peripheral circulatory adjustment or the fact that these mechanisms have already been used to their limit. We observed, however, that patients who have emphysema without "cor pulmonale" appear to need an increase in "central" blood volume in order to maintain cardiac output. This suggests the presence in all our patients of an impaired cardiac response, as though the artificial ventilation, by a mechanism not clear to us, would inhibit a sympathetic cardiac adaptation. This idea is supported by the observation that the mean circulation time is delayed in the patients of the three groups studied, as well as in the patients reported upon by Feinsilver.[19]

Summary

Hemodynamic and respiratory studies were carried out in patients with neurogenic respiratory paralysis or chronic pulmonary emphysema (some of them with "cor pulmonale" in congestive failure) who were subjected to artificial mechanical ventilation.

Cardiac output generally decreased in patients with chronic respiratory paralysis and in all patients with "cor pulmonale" in congestive failure. In patients with chronic pulmonary emphysema, blood flow did not change. Mean circulation time was increased in almost all cases, whereas changes in "central" blood volume took the same direction as the modifications in cardiac output.

Transmural pulmonary arterial pressure decreased in the 3 patients with chronic respiratory paralysis in whom it was measured, and in the only patient with chronic "cor pulmonale" in congestive failure in whom it was determined. A patient with myasthenia gravis in paralytic crisis was subjected successively to artificial ventilation with the iron lung and with positive pressure apparatus, showing minor changes in the variables studied.

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mental in enhancing cardiac output through increased diastolic length of myocardial fibers.

The group with overt signs of "cor pulmonale," 3 of whom (Cases 16-18) were in congestive failure at the time of the study, showed a very outstanding decrease in cardiac output. A delay in mean circulation time tends to diminish a concomitant fall in "central" blood volume. In the 2 patients in whom the changes were most evident, control cardiac output was higher than normal. Several hypotheses may be proposed to explain these facts. In the first place, it is possible that the condition which made necessary the level of cardiac output found in the resting state may have changed. Anoxemia, which was present in all cases, is believed to be a factor of increased cardiac output in "cor pulmonale." Although oxygen saturation was somewhat increased in all cases, in only one (Case 15) did the amount of this change (+8 per cent) seem to be of some possible significance. It might be possible that the decreased oxygen consumption of the respiratory muscles reduces the metabolic load and by that means tends toward a decrease in cardiac output. Partial correction of the retention of carbon dioxide might also collaborate in the same trend. The decrease in cardiac output might also be explained by a decrease in venous return, in which case, one would have to admit that these patients show a diminished venoconstrictor reaction to compensate for the increase in intrathoracic pressure. In addition, it would be necessary also to accept the fact that despite an increase in the residual volume of blood in the heart, the right ventricle is unable to maintain cardiac output when venous return is impaired. Werkö[10] has shown an increase in cardiac output in some patients in congestive heart failure. He considered those patients to be in the descending limb of Starling's curve so that a decrease in venous return and, consequently, in diastolic stretch improved the myocardial ability and returned them to higher cardiac outputs. Present thinking[20-22] attempts to explain these changes by accepting different Starling curves, depending on the responsiveness of the myocardium, sympathetic tone, etc.

Behavior of pulmonary vascular pressures was also different as judged by the 2 patients in whom they were measured—one belonging to each group. The increase in pulmonary arterial pressure and resistance in the patient without "cor pulmonale" (Case 14) in the face of a constant cardiac output is indicative of a primary vascular change. A cause of vasoconstriction is not apparent, whereas the mechanical effects of the positive pressure are difficult to implicate since an increase in transmural pulmonary vascular pressure has been described only in dogs with open chest.[18] In the other case (Case 18) the marked fall in cardiac output in a patient with a restricted vascular bed might be the only cause for returning pulmonary arterial pressure and resistance to normal levels, whereas a decrease in arterial pCO_2 may collaborate by eliminating vasoconstriction.

In the group of patients with chronic respiratory paralysis the need of hyperventilation in order to attain adaptation and a sense of well being was constant. A decrease in blood flow under mechanical ventilation in these patients with quadriplegia and abdominal muscle paralysis might be primarily dependent upon failure of the mechanisms for restoration of venous return, which were interfered with by the positive thoracic pressure. It is noteworthy that muscular rehabilitation in Case 3, obtained in the course of a year, was accompanied by the maintenance of control blood flow when studied at the time (Case 7). Changes in the oxygen saturation of the blood were not significant in these patients, which, furthermore, started from nearly normal values. Since the decrease in arterial pCO_2 which was present in several cases was also visible in the only case in which cardiac output increased, we do not attribute much participation of this factor in those changes. The fall in pulmonary arterial pressure and total pulmonary resistance, which was present in 2 cases (Cases 7 and 8) in which cardiac output remained the same, points either to vasomotion or to a fall in postarteriolar resistance. In the other case (Case 9) in which resistance was maintained the change in cardiac output may be held to be responsible for

An improved transmission oximeter using interference filters

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Oximetry is the measurement of oxygen saturation in whole blood by means of the so-called oximeters. The technique is based on the differential light absorption of oxyhemoglobin (HbO_2) and reduced hemoglobin (Hb) at two different wave lengths. At the wave length of 644 millimicrons (red region) the maximum absorption difference is observed, whereas at 805 millimicrons (near infrared region) the light absorption is equal for both hemoglobins.[1,2] Thus, absorption of light at the red region (R) with regard to the absorption at the infrared region (IR) or "isosbestic point" allows the measurement of the fraction of hemoglobin which is in the form of oxyhemoglobin. The function by which the ratio of the transmissions are related to the percentage of oxygen saturation is defined in the equation:

$$O.S. = \frac{-\log I/I_{O644}}{-\log I/I_{O805}} \cdot \frac{\frac{1}{(e_2 - e_1)d} + \frac{e_3\, C}{e_2 - e_1}}{\frac{1}{e_3\, d}}$$

in which O.S. = oxygen saturation, I = intensity of transmitted light, I_O = intensity of incident light, e_1 = extinction coefficient of HbO_2, e_2 = extinction coefficient of Hb, e_3 = common extinction coefficient of HbO_2 and Hb, C = concentration, and d = depth of cuvette.

But, unfortunately, as indicated by Kramer and associates,[3] whole blood does not obey Beer's law in its strict sense because of variations in the extinction coefficient or changes in concentration. Thus, the relationship between oxygen saturation and the ratio of the logarithm of the transmission yields a family of linear curves for different hemoglobin concentrations.

Several devices for measuring oxygen saturation have been reported,[4-7] but, as mentioned by Wood and Sutterer[8] in their review, since currently available oximeters do not have ideal features, they need the incorporation of many important characteristics for optimal performance. With these recommendations in mind, steps were taken to develop an oximeter, reported on here, in which the characteristics which they specified are fulfilled.[8]

Present oximeter

A cuvette-oximeter for the continuous determination of the oxygen saturation of flowing whole blood is illustrated in Fig. 1. This device consists of (a) two miniature

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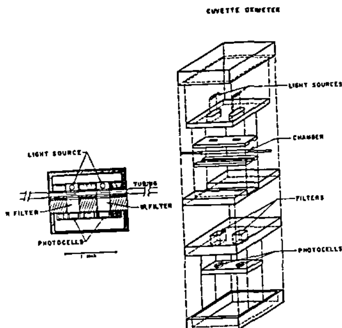


Fig. 1. Cross-sectional view (*left*) of the cuvette-oximeter (to scale). Exploded view (*right*) to show geometrical arrangement of the light sources, chamber, and filter-photocell assembly.

Single scale (*Fig. 4,A*). With switch S_1 in position C, blood is withdrawn through the cuvette at constant rate (5 to 10 c.c. per minute), and the IR potentiometer (R_2) is adjusted to some given deflection, preferably full scale. This setting determines the sensitivity of the single scale. The sampling chamber is then flushed completely with saline solution. Switch S_1 is rotated to position D, and the single-scale galvanometer is brought to its original zero position by advancing the R_6 potentiometer. Once the adjustments are made, when blood is withdrawn through the cuvette-oximeter, the observed deflection is a function of the oxygen saturation.

Double scale (*Fig. 4,B*). With saline solution in the cuvette and the S_1 switch in position D, potentiometers R_3 and R_4 are advanced so that their respective galvanometers are adjusted to have the same deflection, preferably full scale of the recording device. Then blood is withdrawn through the cuvette-oximeter, and the observed deflections are a function of the transmission of light at the two different wave lengths.

Dye curve recording (*Fig. 4,C*). This oximeter can be used as a densitometer. With blood flowing through the cuvette, switch S_1 is rotated to position B, and the potentiometer R_1 is advanced. Because the polarity is reversed, the galvanometer will go off scale. The bucking voltage potentiometer (R_7) is adjusted to bring the galvanometer to its original zero position. Any change in the optical density of the blood produced by the injection of an indicator which absorbs light at 805 mμ will deflect the galvanometer approximately proportionally to the concentration of the dye flowing through the cuvette.

Dynamic response

The over-all dynamic response of the system was tested by using the square wave technique as described by Fox and associates.[11] A 25-cm. tube was attached to the proximal end of the cuvette-oximeter, and blood of two different oxygen saturations was alternately withdrawn at a constant rate of 50 ml. per minute. The 90 per cent response time for a change in oxygen saturation from 95 to 40 per cent is less than 0.15 second.

light sources* powered by means of an 8-volt constant power supply, (b) a sampling chamber, and (c) a filter-photocell assembly.

The sampling chamber consists of a piece of nylon tubing† flattened to an ellipsoidal shape by means of two aluminum plates in which windows have been milled to allow passage of the light beam. The windows are 1/16 inch wide and ¼ inch long, spaced ¼ inch apart. The slots are purposely made narrow compared to the total width of the compressed tube; thus, the light beam passes only through the center, uniformly flat portion of the chamber. The thickness of the chamber is 0.7 mm. The volume of blood under each window is approximately 0.02 c.c. The dead space of the tube is reduced to a minimum (0.5 ml.). B-D Luer Lok connectors are attached at the inlet and outlet of the tubing.

The filter-photocell assembly consists of a red interference filter‡ with 644 millimicrons peak wave length, and an infrared interference filter‡ with 805 millimicrons peak wave length. Immediately behind the red filter a photocell Cl-407L‡ has been mounted; similarly, there is a Cl-404L cell behind the IR filter. The IR filter is mounted in a tilting mechanism[9] to allow proper adjustment of the wave length. Fig. 2 illustrates the spectral response of the filters and photocells in the present oximeter with regard to the oxygenated and reduced hemoglobin.

Fig. 3 illustrates the circuit diagram of the control unit. Switch S_1 is a 6-position wafer type that selects each of the functions.

Position A: zero. The output is grounded so that the mechanical zero of the galvanometers may be checked or the recorder adjusted to zero.

Position B: dye curve recording. The IR cell is connected through potentiometer R_1 to the single-scale galvanometer with the polarity reversed. The other side of the galvanometer is fed through a potentiometer R_7 with a variable bucking voltage to adjust the galvanometer to zero.

Position C: infrared setting. The double-scale circuit is grounded. The single-scale galvanometer is connected to the IR cell through potentiometer R_2. The other side of the single-scale galvanometer is connected to a zero suppression circuit through R_8. In a large-scale recorder this circuit may be avoided, but when small-scale recorders are used, this zero suppression circuit represents an advantage because it is possible to expand the single scale over a small range of saturations, making the reading error of lesser magnitude.

Position D: saturation. The double-scale circuits are *ON*. The double-scale IR and R galvanometers are connected to the IR and R photocells through potentiometers R_3 and R_4, respectively. The single-scale galvanometer is connected as in D, except that the zero suppression voltage is replaced by the R cell output through potentiometer R_6.

Position E: single scale off. The single-scale galvanometer is grounded for checking zero or eliminating the single-scale reading. The double-scale circuit is connected as in D.

Position F: double scale off. The double-scale circuit is grounded either to check zeros or to eliminate the double scale from recording, while the single scale is connected as in D.

Resistors R_r and R_{ir} are shunt resistors placed across the red and infrared potentiometers to adjust the span of the output voltage and are selected according to the sensitivity of the galvanometers or the recording system used.

Operation

The principle of operation is basically that described by Wood,[10] which allows the use of single-scale and double-scale recordings. For the single-scale reading, the differential output of the photocells is recorded, whereas for the double scale the output of each photocell is recorded separately.

The operation of the circuits can be best understood by considering each of the functions individually. The basic schematics of the functions are illustrated in *A*, *B*, and *C* of Fig. 4.

*Type 6318-680, Chicago Miniature Lamp Works, Chicago, Illinois.

†Nylaflow Tubing, O.D. = 0.125 inch, I.D. = 0.096 inch. Almac Plastics, New York, N. Y.

‡Baird Atomic, Inc., Cambridge, Mass. Interference filters (B-9 type), size 5/16 square inch.

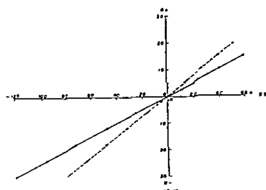


Fig. 5. Illustrates the correlation between I-IR double-scale difference and single-scale deflection at two given sensitivities.

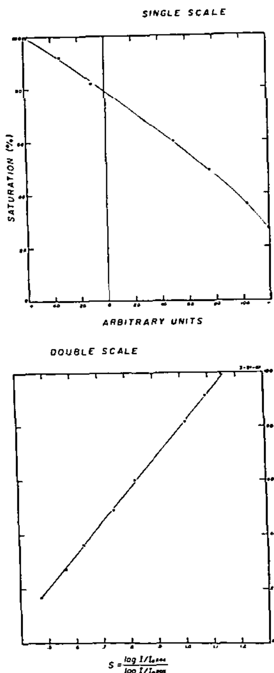


Fig 6. Shows empirical calibration curves for single and double scale.

Correlation between single and double scales

The single scale is the differential output of the R and IR cells, whereas the double scale is the output of the R and IR cells taken separately. When IR and R cell outputs are equal, that is to say, in a ratio of 1, the single-scale output is zero. For a positive difference (R > IR) the single scale deflects above zero (increased oxygenation), whereas for a negative difference (R < IR) the single scale deflects below zero (decreased oxygenation). As illustrated in Fig. 5, the R and IR differences are plotted in the vertical scale; the IR reading of the double scale coincides with the zero of the single scale. For a given difference of the R and IR of the double scale there will be a proportional deflection of the single scale depending on whether the difference is negative or positive, but keeping a linear relation for a given change. If the sensitivity of the single scale is changed, the slope of the curve is changed. This is illustrated by the solid and broken lines in the diagram. Empirically, the mechanical zero of the single scale should be set at an approximate value of 75 per cent saturation.

Calibration

Empirical calibration curves of the single and double scales were constructed from data derived from 7 dogs and 63 human subjects breathing room air and undergoing cardiac catheterization. Samples of blood were withdrawn from various sites of the circulatory system through the cuvette-oximeter, at a rate of 10 to 15 c.c. per minute; and while oximetric recordings were made, the blood was collected in heparinized syringes for determination of saturation by the Van Slyke-Neill method.[12] The galvanometric deflections were recorded by a polygraph. The single-

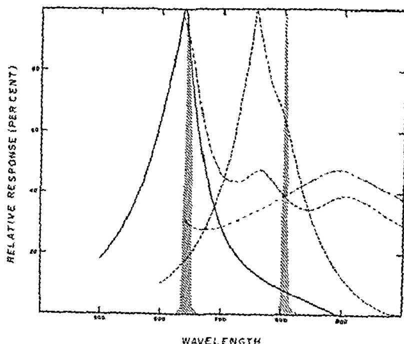


Fig. 2. Spectral response curves of R and IR photocells (*solid and broken lines, respectively*). Shaded area shows peak wave length of respective interference filter —— and – – lines represent spectral curves of HbO_2 and Hb, respectively.

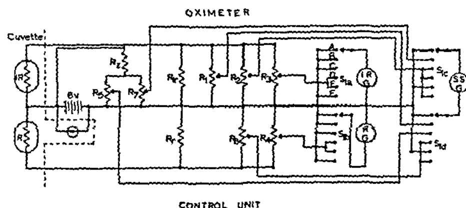


Fig. *3.* Illustrates the circuit diagram for single and double scales.

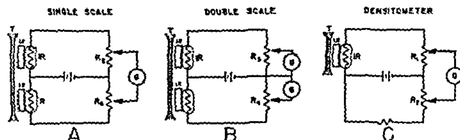


Fig. 4. A, Principle of operation of single scale. *B,* Principle of operation of double scale. *C,* Principle of densitometer.

degree of reproducibility is such that any flow rate above the critical value will give the same results. Stationary flow in the cuvette changes (slightly) the deflections because of settling effects which affect the transmission of light.

One of the disadvantages of the present design is that nonidentical calibration curves are obtained from different units, probably because of the nonuniformity of the chamber thickness and the variation of electrical output from the photocells. Also, there are slight differences due to changes in the incident light striking the photocell, because of the position of the photocell with respect to the chamber window. Another problem involving mainly the red-cell output is the effect of reflection of light by the wall of the tubing. Maximum scattering of light and minimum reflection greatly improves the sensitivity of the red cell.

Summary

An oximeter using monochromatic light is described, and data are presented which reveal the accuracy of determinations made by the oximeter as compared with the Van Slyke method of analysis. The standard error of this comparison was ±0.2 per cent in the range of hemoglobin concentration from 10 to 17 Gm. per 100 ml.

Also, the present cuvette-oximeter allows continuous recording of dye concentration for use in indicator-dilution curves for measurement of blood flow.

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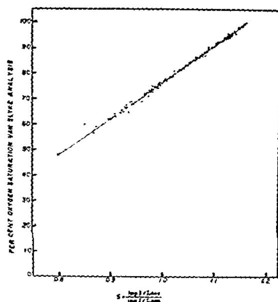


Fig. 7. This figure illustrates the correlation between the saturation obtained by the Van Slyke analysis method and the double-scale optical density ratio.

scale deflection, in millimeters, and the ratio of the log of the double-scale deflections were plotted against the corresponding value of oxygen saturation by the Van Slyke method. Fig. 6 illustrates a typical calibration curve for the single and double scales. As can be noted, the single-scale deflection, in millimeters, is nonlinear with respect to the oxygen saturation values, whereas the double-scale is linear over the entire range recorded in this experiment.

Fig. 7 illustrates the range of saturation obtained with the Van Slyke method plotted against the double-scale optical density ratio in 63 patients undergoing cardiac catheterization while breathing room air. The ages of the patients varied from 2 months to 64 years. In some cases, because of the fast response of the system, the recordings showed variations due to respiration. With the assumption that the sample analyzed by the Van Slyke method is an integrated value of the variations, the areas of the recorded curves were integrated to give a mean value, and the results were plotted against the saturation by the manometric technique. Since the rate of withdrawal was constant, this seems to be a reasonable assumption.

The values observed for oxygen saturation in human subjects varied from 48 to 100 per cent. The greatest differences between the oximetric and the Van Slyke methods were +5.2 and −6.6 per cent. The standard deviation was 2.1 per cent, and the r value for correlation between the two methods was +0.558 ($p < 0.001$). In the whole group the oximeter overestimated the saturation value by an average of 0.2 per cent in 133 determinations. In the experiments on dogs, much lower saturations were obtained in order to check the linearity of the system. However, the results were similar to those found in the human subjects.

Discussion

The present oximeter allows measurement of oxygen saturation in small quantities of flowing whole blood.

The degree of stability is better than 0.02 per cent of full scale per minute. The photocells are not affected by changes in barometric pressure or humidity or harmful vapors. However, changes in temperature due to heat radiating from the light sources, as well as possible self-heating, affect their stability. This problem is circumvented by dissipating the heat from the light sources and thermoinsulation of the photocells from the body of the cuvette.

Improvement of performance characteristics has been achieved by introducing the use of monochromatic light. This provides constancy of wave length as well as linear relationship between oxygen saturation and the logarithm of the light transmission at the wave lengths used.

The present cuvette-oximeter does not require electronic amplification, and the output voltage can be adjusted by means of shunt resistors to drive fast-frequency galvanometers or can be used in conjunction with direct-writing recorders of suitable sensitivity (50 mv. full scale).

The measurements by the R and IR photocells are not made simultaneously on identical portions of the sample of blood; however, the cells are in very close proximity, and we assume that they are representative measurements of identical portions of blood if rate of blood flow is kept constant.

Above a critical value (5 to 10 c.c. per minute) the present oximeter is not affected by fluctuations in flow rate, and the

right anterior oblique position, and a cuffed endotracheal tube was inserted. Air was collected in a Tissot spirometer attached to the endotracheal tube by an appropriate series of flutter valves, a three-way stopcock, and low-resistance rubber tubing. A 150-liter bag of 15 per cent nitrous oxide, 21 per cent oxygen, and 64 per cent nitrogen was attached to the stopcock so that at an appropriate time the mixture could be administered to the dog. Four cardiac catheters were placed in the animals: one in the pulmonary artery, one in the coronary sinus, and two in the right atrium. One of the catheters in the right atrium was used for measuring central venous pressure; the other, for infusion of the adenine nucleotide. A Cournand needle was placed percutaneously in the femoral artery and attached by plastic tubing to a manifold for rapid consecutive sampling of blood. Pressures from the pulmonary artery, right atrium, and femoral artery were recorded through Statham strain gauges on the Gilson macropolygraph. Cardiac output was measured by the Fick principle, whereas the coronary blood flow was measured by the nitrous-oxide saturation technique, assuming a partition coefficient of 1 between blood and heart. Analyses of blood gas were made by the Van Slyke-Neill method. Expired air was analyzed for oxygen and carbon dioxide by the method of Scholander. Analyses of the blood for nitrous oxide were made by the method of Orcutt and Waters.

In all cases, control observations of cardiac output and coronary blood flow were made. The animals were then infused with the agent under study by means of a constant-injection syringe (Harvard Apparatus Company) which delivered the solution into the right atrium. Infusion was begun 5 minutes before study of the cardiac output was started, and was continued for a total of approximately 20 to 25 minutes, during which time the cardiac output and the coronary blood flow were determined. In some experiments the oxygen saturation of the coronary sinus blood was monitored during infusion of these agents and was found to increase rapidly and remain at a reasonably steady plateau until the infusion was stopped; then it quickly fell again to approach control values. Some studies were done with the dog's heart exposed so that the coronary vessels and the color of the myocardium and coronary venous blood could be observed. In some animals, coronary arteriography was accomplished by cannulation of the coronary arteries through the aorta under fluoroscopy. Coronary arteriograms were taken utilizing the Westinghouse intensifier before and during infusion of adenosine triphosphate (ATP).

In the studies of ATP, several different doses were used. The major portion of the study was conducted with the sodium salt of ATP—of this substance, 1 animal received 0.08 micromoles per kilogram per minute; 2 received 0.2 micromoles per kilogram per minute; 1 received 1 micromole per kilogram per minute; 12 received 2 micromoles per kilogram per minute; 1 received 3 micromoles per kilogram per minute; and 2 received 4 micromoles per kilogram per minute. There appeared to be a threshold dose which would elicit a response in the coronary circulation, and, in general, this dose was near 2 micromoles per kilogram per minute. For no apparent reason, in two studies this dose appeared to be inadequate. In some instances, when the initial dose was inadequate, if it were increased to a higher level, the agent would become an effective coronary vasodilator, as judged by the change in the color of the coronary sinus blood.

The dose of adenosine was 2 micromoles per kilogram per minute, administered in the same fashion as ATP. Eleven complete studies were done in the adenosine series, and the data are presented in Table II. Three studies were made concerning the effects of inosine 5′ phosphate. In one study a small dose was given, and in two the usual dose of 2 micromoles per kilogram per minute was used. These results are in the miscellaneous group at the bottom of Table I.

Results

The results are summarized in Tables I and II* for the effective dose of 2 micromoles per kilogram per minute. The data

*Complete tables are available from the A.D.I., Auxiliary Publications Project, Photo Duplication Service, Library of Congress, Washington 25, D. C.

The systemic and coronary hemodynamic effects of adenosine triphosphate and adenosine

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Various adenine nucleotides, particularly adenosine and its phosphorylated derivatives, are known to be potent vasodilators.[1-6] Previous experiments have indicated that, in the nonintact animal preparation, administration of these agents into the coronary circulation has been associated with a considerable increase in coronary blood flow.[2,3,6,7] It appeared to be worth while, however, to reinvestigate these agents in the intact specimen by the nitrous-oxide method. It was hoped that this would clarify whether the increase in coronary flow which has been reported is due to introduction of the agent directly into the coronary circulation in a higher concentration than occurs in the systemic vessels, or whether the agents are specific coronary vasodilators and have similar effects when administered into the systemic circuit so that the concentration in the coronary circulation is similar to that in the rest of the body. It is pertinent at this point to consider that nitrites administered into the coronary vessels of nonintact animals increase coronary blood flow,[8] whereas systemic administration of a longer acting nitrite to man has shown no real change in coronary blood flow.[9] Moreover, it was thought that information obtained in intact animals might furnish a better experimental background for hemodynamic trial of these potent coronary vasodilators.

Material and methods

A series of experiments was done in dogs which weighed between 15 and 30 kilograms. The plan of study was the same in all animals, although different agents were administered. Fasting dogs were given 3 mg. per kilogram of body weight of morphine sulfate, subcutaneously, followed in 1 hour by an anesthetizing dose of 0.25 ml. per kilogram of a mixture of 50/50 veterinary pentobarbital and Dial-urethane.* When anesthesia was secured, the dogs were placed on a dog board in the

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*Furnished through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, N. J. Contains 100 mg. of Dial, 400 mg. of monoethylurea, and 400 mg. of urethane per milliliter. Veterinary pentobarbital contains 60 mg. of sodium pentobarbital per milliliter.

Table II. Systemic and coronary hemodynamic effects of adenosine

Parameter	Control	Study	% Change	p Value <
Heart rate (beats/min.)	93	153	+65 6	0 001
Mean arterial blood pressure (mm. Hg)	114	104	−8 8	0 05
Mean pulmonary arterial blood pressure (mm. Hg)	13	13	0 0	0 1
Mean right atrial blood pressure (mm. Hg)	2.4	1.5	−41.7	0 1
Minute volume of respiration (L./min.)	2.0	2.7	+35.0	0.01
Oxygen consumption (ml./min.)	104	122	+17.3	0.1
Respiratory quotient	0.85	0.89	+5.9	0.02
Arterial-venous oxygen difference (ml./100 ml. of blood)	4.1	3.3	−19 5	0.05
Coronary sinus oxygen content (ml./100 ml. of blood)	5 8	14 0	+141 4	0.001
Arterial hematocrit (%)	47	46	−2 1	0.1
Femoral arterial pH	7 23	7.26	+0 4	0 01
Coronary sinus pH	7 19	7 24	+0 7	0.001
Cardiac output (L./min.)	2 6	3.8	+46 2	0.001
Total peripheral resistance (c g s. units)	3740	2275	−39.2	0.01
Total pulmonary resistance (c.g.s. units)	406	287	−29 3	0 001
Left ventricular work (Kg.M./min.)	3 9	5 3	+35 9	0 01
Right ventricular work (Kg.M./min)	0 5	0 7	+40 0	0.01
Coronary blood flow (ml./100 Gm./min.)	91	613	+573.6	0.02
Left ventricular oxygen usage (ml./100 Gm./min.)	10.5	22 4	+113 3	0.1
Coronary vascular resistance (units)	1.30	0 28	−70 8	0.001
Index of efficiency (LVW ÷ LV O_2 usage)	0 39	0.32	−17 9	0.2

venous oxygen difference. The coronary sinus blood oxygen content was markedly increased by both adenosine and ATP, with considerable narrowing of the arterial-coronary sinus oxygen difference. Simultaneously, the coronary sinus carbon-dioxide content decreased markedly, with very great narrowing of the coronary sinus-arterial carbon-dioxide difference. In animals receiving ATP there were significant increases in both hemoglobin and hematocrit; however, no significant change occurred in these parameters with adenosine. Cardiac output was significantly increased by administration of both agents, and, although the left ventricular work increased with both agents, the increase was not statistically significant with ATP because of the greater reduction in mean arterial blood pressure with this agent. Right ventricular work was somewhat increased by both agents, but this increase reached statistical significance only during administration of adenosine. Total peripheral and total pulmonary vascular resistances were significantly reduced by each agent.

As seen in the tables, both agents produced striking increases in the coronary blood flow, accompanied by an increase in

Table I. Systemic and coronary hemodynamic effects of sodium adenosine triphosphate

Parameter	*Control*	*Study*	*% Change*	*p Value <*
Heart rate (beats/min.)	76	131	+72.4	0.001
Mean arterial blood pressure (mm. Hg)	116	100	−13 8	0.001
Mean pulmonary arterial blood pressure (mm. Hg)	14	12	−14.3	0.01
Mean right atrial blood pressure (mm. Hg)	3 6	1.5	−58.3	0.001
Minute volume of respiration (L./min.)	2.3	2 8	+17.4	0.05
Oxygen consumption (ml /min)	104	105	+1.0	0 4
Respiratory quotient	0 83	0 90	+8 4	0 05
Arterial-venous oxygen difference (ml /100 ml. of blood)	4 4	3 4	−25 0	0.02
Coronary sinus oxygen content (ml./100 ml of blood)	5 5	15 0	+172.7	0.001
Arterial hematocrit (%)	44	46	+4 5	0.01
Femoral arterial pH	7 25	7 27	+0 3	0 01
Coronary sinus pH	7 21	7 26	+0 6	0 001
Cardiac output (L /min.)	2 4	3 3	+37 5	0.01
Total peripheral resistance (c.g.s. units)	4052	2549	−37 1	0 01
Total pulmonary resistance (c.g s. units)	503	297	−40 8	0 01
Left ventricular work (Kg M /min.)	3 9	4 4	+15 4	0 2
Right ventricular work (Kg M /min.)	0 4	0 6	+25 0	0.2
Coronary blood flow (ml./100 Gm./min)	73	464	+534 2	0 001
Left ventricular oxygen usage (ml./100 Gm /min.)	8 3	12 3	+48 2	0 1
Coronary vascular resistance (units)	1 69	0 27	−84 0	0.001
Index of efficiency (LVW ÷ LV O_2 usage)	0 47	0 37	−21 3	0 05

hereinafter described, unless stated otherwise, represent the studies of ATP and of adenosine which were analyzed statistically and are presented in Tables I and II. Both administration of adenosine and effective doses of ATP were accompanied by considerable increase in cardiac rate. Whereas mean systemic arterial blood pressure decreased significantly with both agents, the pulmonary arterial blood pressure decreased with ATP but not with adenosine. Mean right atrial blood pressure decreased with both agents; however, the decrease was more variable with adenosine and did not reach statistical significance. Administration of both agents was associated with an increase in minute volume of respiration accompanied by an increase in carbon-dioxide elimination; however, the oxygen consumption did not change and, consequently, the respiratory quotient rose. Undoubtedly associated with the hyperventilation were clear-cut increases in arterial and coronary sinus blood pH as well as reductions in the mixed venous and arterial carbon-dioxide content. The arterial oxygen content increased significantly in both studies, as did the mixed venous oxygen content, with significant narrowing of the arterio-

effective as adenosine in increasing coronary blood flow.[7] This discrepancy may be related to the fact that ATP is at least partially dephosphorylated before reaching the myocardium unless given directly into the coronary vessels themselves. Such a hypothesis is consistent with the observation that removal of two phosphate groups from ATP significantly reduces its coronary vasodilator action.[6,7] They are also compatible with observations that infusion of up to 2,000 micromoles per minute of ATP into one brachial artery is associated with a marked increase in the blood flow in the forearm on the homolateral side, but with no change in the blood flow in the forearm on the contralateral side. These results were accepted as evidence for rapid breakdown of ATP in vivo.[11] The present observations of the relative inactivity of inosine 5′ phosphate also agree with the previous demonstration in nonintact specimens that the 6 amino group is required for activity of these compounds.[5,7]

The decrease in coronary vascular resistance is roughly twice as great as the reduction in peripheral vascular resistance in the present experiments. Since the compounds were given into the right atrium, there is no reason to believe that the concentration of the agent is significantly different in the coronary than in the systemic circuit. Therefore, it seems clear that the agents are relatively much more active in the coronary circulation than in the body as a whole. Although the compound is an effective vasodilator in peripheral muscular beds,[4] whether it is more or less effective than in the cardiac muscle bed is another question, and is not answered by these experiments. Since the arteriovenous oxygen difference across the myocardium narrowed markedly because of a rise in the coronary sinus oxygen content, and since the coronary sinus carbon-dioxide content decreased significantly, the agents most probably do not produce vasodilatation through either hypoxia or accumulation of metabolites. Whether the vasodilatation is due to action of the vasomotor nerves or the vessel wall is not clarified.

For many years there has been speculation as to whether the adenine nucleotides are the physiologic mediator in increasing coronary flow and producing vasodilatation in response to muscular exercise.[4,12] The apparent difficulty in proving this thesis is that such a small quantity of ATP is active that it has not been possible to detect it by chemical testing of the blood.[4] Surely, the compound is sufficiently active to bear further consideration in this role. In addition, observations of the activity of these agents in the coronary circulation of man seem highly desirable.

Conclusions

1. The systemic and coronary hemodynamic effects of adenosine, adenosine 5′ triphosphate, adenosine 5′ diphosphate, and inosine 5′ phosphate have been tested in the intact anesthetized dog, using the Fick principle for determination of cardiac output and the nitrous-oxide method for measurement of coronary blood flow.

2. Adenosine triphosphate, adenosine diphosphate, and adenosine were found to be very active compounds, whereas inosine phosphate was not.

3. The active compounds were associated with an increase in heart rate, cardiac output, coronary blood flow, coronary sinus oxygen content, and myocardial oxygen consumption. Systemic arterial pressure tended to be reduced.

4. There were marked reductions in the total peripheral and coronary vascular resistances. However, the decrease in coronary resistance was considerably greater than the decrease in peripheral resistance, and the increase in coronary blood flow was strikingly greater percentagewise than the increase in cardiac output.

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the calculated myocardial oxygen consumption and marked decreases in the coronary vascular resistance. Cardiac efficiency was significantly reduced by ATP and variably, but not significantly, decreased by adenosine.

Dipotassium ATP seemed to be an active coronary vasodilator as judged by the limited number of observations made; it produced a considerable increase in coronary blood flow in two of three trials. Sodium adenosine diphosphate was active in one trial. It was clear that, in similar dosage, inosine 5′ phosphate did not have the same effects on the systemic or coronary hemodynamics.

Discussion

It is apparent from the data presented and from the literature that both adenosine and adenosine triphosphate (ATP) have marked hemodynamic effects when administered to anesthetized experimental animals. Not only are the systemic hemodynamic effects of vasodilatation and increased cardiac output remarkable, but the coronary hemodynamic changes in nonintact specimens are striking.[2,3,6,7] It should be indicated that in many of the studies in the present series the increase in coronary blood flow was so great that the nitrous-oxide curves approximated each other very quickly and the coronary flow could not be calculated with great accuracy. However, there was no doubt that a marked increase in coronary flow had occurred during the experiment, both from the nitrous-oxide curves and because of marked increase in coronary sinus blood oxygen content. Furthermore, direct viewing of the heart during infusion of ATP revealed the opening up of vessels not previously visible, with a change in the color of the coronary venous blood from very dark to brighter red and a considerable increase in the redness of the myocardium. In addition, coronary cineangiocardiography revealed an increase in the size of the coronary vessels during infusion of ATP. Such changes are consistent with diffuse vasodilatation rather than the opening of shunts between vessels.

It is interesting to observe that previously reported studies, utilizing the rotameter, revealed a remarkable increase in myocardial oxygen consumption subsequent to the administration of these agents into the coronary arteries.[7] The increase was similar to that shown here. Cardiac efficiency was reduced significantly during administration of ATP, and decreased somewhat but not significantly by adenosine. The heart rate was increased considerably by both agents. It is well known that an increase in cardiac rate is associated with an increase in coronary blood flow and myocardial oxygen consumption, as well as a decrease in cardiac efficiency.[10] However, in this study the increase in coronary flow with both the administration of adenosine and ATP was much greater than that which occurred in the previous study of cardiac acceleration, even though the increase in rate was less here than in the acceleration study.[10] Hence, the vasodilatation was not due to change in rate alone. The early experimental demonstration that adenine nucleotides produce slowing in cardiac rate[1] is not reflected in the present data, apparently because of a difference in dose, since it was possible to produce marked bradycardia in the dogs by increasing the rate of administration of ATP. The dose required to produce such bradycardia was not carefully quantitated.

The present results extend and confirm, in general, those observations reported previously and obtained by utilizing the heart-lung preparation,[1] Langendorff perfusion,[2] the Morawitz cannula,[3] and the rotameter.[6,7] They may also be of greater interest since the compound was administered systemically so that all vascular beds except the lung were exposed to a similar concentration of the active compound, instead of the coronary vessels alone having an artificially selective concentration. It is of interest that adenosine was reported to have a greater effect on heart rate and coronary blood flow, whereas phosphorylated derivatives lowered the blood pressure more.[5] It will be recalled that, in the present study, ATP lowered the systemic arterial blood pressure more than did adenosine, whereas the increase in coronary flow was roughly comparable with the two agents. The present results and those just discussed[5] are both at variance with the report that ATP was four times as

The effects of "dry" heat on the circulation of man. Renal hemodynamics

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It has been well established that serious stresses may be imposed on the circulation of man by either sudden[3,6] or prolonged[1,2] exposures to a warm and humid environment. However, comprehensive data which would define solely the hemodynamic effects of an acute, short-term exposure to a warm and relatively dry environment in nonacclimatized man have not been available heretofore. Such determinations might serve as a point of departure in further assessment of the reactions of man to heat under a variety of environmental circumstances.

In previous communications we have presented general and splanchnic hemodynamic data collected during a 2-hour exposure to "dry" heat (98 ± 1°F. and 40 per cent relative humidity) of resting normal subjects[18] as well as patients with enlarged left ventricles, compensated and in failure.[15,18] The significant findings were decreases in the brachial and pulmonary arterial pressures, in the systemic, total pulmonary, and splanchnic vascular resistances, and in the calculated left ventricular work, without changes in the cardiac output or the splanchnic blood flow.

The purpose of the following report is similarly to delineate the gross changes in renal hemodynamics that may occur in subjects who have various medical disorders, but who are free of heart disease, as well as in those with heart disease in whom the sole cause lay in factors which burdened initially the left ventricle. Standard renal clearance techniques were employed. The control data were gathered at the comfortable environment of 73°F. ± 1 and a relative humidity of 40 per cent ± 3.

Materials and methods

Forty hospitalized patients were studied at random and divided into four equal groups. Group A consisted of patients who were convalescent from various medical diseases. Two of these subjects had rheumatic and coronary artery heart disease, respectively. One of them was in combined ventricular failure. Two sets of determinations of the glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF) were carried out only in the comfortable environment at an interval of 2 hours. These data served as the control determinations for the method. Group B

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pressure by Statham strain-gauge transduction on a direct-writing oscillograph. Central venous pressures were similarly inscribed when cardiac catheterization was performed. Samples of urine were collected from an indwelling urethral catheter at three successive 10-minute intervals. Samples of blood were obtained before the priming infusion and at the fourth minute of the first and third collection periods. Plasma and urine were analyzed for para-aminohippurate and mannitol by the methods of Page and Corcoran.[13] All clearance rates were expressed in terms of 1.73 square meters of body surface area. Effective renal blood flow (ERBF) was derived from renal plasma flow and hematocrit values. "Total" renal vascular resistance (RVR) was expressed as the ratio of mean brachial arterial pressure to ERBF. Filtration fraction (FF) represents the ratio of GFR to ERPF × 100. Mean brachial arterial pressure was calculated by planimetric integration of suitably inscribed pressure pulses.

A sample of blood for the determination of blood urea nitrogen was drawn prior to the experiment. Values to 18 mg. per cent were considered to be normal.

After the initial establishment of steady state, control determinations were made at the comfortable environment of 73°F. and 40 per cent humidity, and repeat observations were made at the end of 2 hours of exposure to the warm environment. The subjects lay quietly recumbent and were covered only with small towels throughout the procedure.*

Results

The individual data for the four groups are presented in Tables I through IV. Averages, percentile changes, and significance analyses (Fisher's "t" test, groups less than 30) are summarized in Table V.

*It is recognized that the renal clearance techniques employed cannot detect rapid fluctuations which might occur in the experimental design as presented However, previous studies have shown that the general[15] and splanchnic[18] hemodynamic changes which occur at the end of 1 hour of exposure to 98° F. and 40 per cent humidity do not differ from those noted at the end of 2 hours. Therefore, it is believed that the clearance values obtained at the end of 2 hours of warm exposure represent a valid average new steady state.

Filtration and flow rates were, on the whole, lower in these patients than those for normal people reported by Goldring and Chasis.[8] This can justifiably be accounted for in that, generally, we were dealing with an older age group of hospitalized patients who were on restricted activity or almost complete bed rest, a barbiturate was employed for sedation,[9] and most of the patients were women.[8] Indeed, average FF base lines for Groups A, B, and C were 20, 20, and 21, which are in close agreement with the value of 20 ± .03 for normal subjects reported by Goldring and Chasis.[8] In Group D, the average base-line FF was 25, as would be expected from the inclusion of at least 5 subjects who either had recently been or still were in right-sided congestive failure at the time of study. Three of these (H.B., V.T., and R.T.—Table IV) had filtration fractions of 31, 31, and 35, respectively.

In addition, a number of patients in Groups C and D had clinical evidence of chronic inflammatory renal disease. The blood urea nitrogen was abnormally elevated in L.R. (Table III, 46 mg. per cent), L.H., and R.T. (Table IV, 35 and 23 mg. per cent). This would be expected to result in inordinately low clearance values, which are recorded with reservations. However, any changes induced by the experimental procedure may reasonably be considered to be valid.

The control subjects (Group A) demonstrated no changes in the various measurements which were made, except for a slight but significant rise in the brachial arterial pressure.

All groups of patients exposed to heat demonstrated a significant rise in the heart rate and a fall in the blood pressure. GFR, ERBF, and FF remained unchanged, and RVR decreased significantly in the normal patients and in those with enlarged left ventricles not in failure.

In the subjects of Group D, who were in left ventricular failure, ERBF and GFR showed small but significant decreases without a change in the filtration fraction. The decrease in GFR was also significant when compared to that of the control subjects.

The average RVR did not change in

Table I. Individual data for 10 subjects with normal hearts in whom all determinations were made at 73°F. and 40 per cent humidity

Patient *Age*	*Race, Sex, B.S.*	*Diagnosis*		*Heart rate*	*PBA*	*ERBF*	*GFR*	*FF*	*RVR*
J.A.*	W, F	Rh.H.D; aortic and mitral	C	58	148/62 (97)	757	89	21	.128
65	1.56	insufficiency, III	2 hr.	55	152/63 (97)	799	93	21	.121
R.R.**	N, F	Coronary H D., IV	C	54	142/70 (88)	349	47	24	.252
70	1.58		2 hr.	44	153/72 (92)	369	46	22	.249
F.P.	N, F	Possible connective tissue	C	87	125/75 (98)	827	110	23	.119
39	1 63	disease	2 hr.	90	131/80 (101)	691	108	27	.146
B.C.	W, F	Essential hypertension; alcoholic neuropathy	C	113	158/114 (132)	551	60	17	.240
34	1 53		2 hr.	108	168/119 (140)	531	57	17	.264
F.R.	N, F	Laennec's cirrhosis, mild	C	78	105/71 (86)	1,049	122	18	.082
36	1 73		2 hr.	73	117/78 (95)	1,046	124	18	.091
E.K.	N, F	Cerebral thrombosis; recovered	C	76	156/97 (124)	456	72	25	272
65	1 70		2 hr.	78	157/100 (126)	496	72	23	.254
W.H.	N, F	Chronic alcoholism	C	86	98/69 (82)	544	62	17	.151
41	1 58		2 hr.	91	108/80 (91)	617	58	14	.147
P.G.	N, F	Essential hypertension, labile	C	59	158/87 (106)	533	65	20	.199
47	1 54		2 hr.	62	180/95 (129)	526	76	23	.245
B.R.	W, F	Duodenal ulcer	C	62	105/61 (81)	582	58	16	.139
47	1 64		2 hr.	70	119/65 (91)	580	56	15	.157
K.L.	N, F	Sarcoidosis	C	82	107/61 (80)	1,017	107	18	.079
39	1.67		2 hr.	80	109/65 (81)	984	101	17	.082

*Pressure in the right ventricle and the pulmonary wedge pressure were normal.
**Pressure in the right ventricle 46/14 mm. Hg
PBA Brachial arterial pressure (mm.Hg); the mean pressure is given in parentheses *ERBF*: Effective renal blood flow (c.c./min./1.73 M²). *GFR*: Glomerular filtration rate. *FF*: Filtration fraction. *RVR*: Renal vascular resistance (mean brachial arterial pressure/ERBF). *C* and *2 hr.*: Determinations obtained initially and at the end of 2 hours, respectively

was comprised of patients with normal hearts. Group C consisted of patients with enlarged left ventricles who were compensated at rest. Group D was comprised of subjects who were in left ventricular failure at the time of study. When doubt existed as to the status of left ventricular compensation, cardiac catheterization was carried out prior to the initial measurements of renal clearances. Resting pulmonary wedge pressures above 12 mm. Hg were assumed to indicate the existence of left ventricular failure.

All medications except digitalis were discontinued at least 1 to 2 days prior to the tests. Studies were performed in the morning when the patients were in the postabsorptive state. Water was given by mouth in a quantity sufficient to insure a flow of urine greater than 2 ml. per minute. Pentobarbital sodium, 0/1, was given to allay the restlessness and increased motor activity which is frequently observed during prolonged laboratory procedures.

Effective renal plasma flow and glomerular filtration rate were measured from the plasma clearances of sodium para-aminohippurate and mannitol, employing a constant-infusion pump, by the method of Goldring and Chasis.[8] An indwelling needle in the brachial artery served for the recovery of samples of blood and the recording of the direct arterial

cantly and progressively with increased duration of exposure. However, these subjects were moving about, and exercise, particularly in a hot environment, is known to decrease GFR and ERPF.[12,17] It is also noteworthy that the lesser degrees of reduction were found in the 6 subjects who were studied by the single-injection technique and voluntary micturition, as compared to the subjects who had continuous infusion and an indwelling catheter. This suggests that emotional factors[16] related to the more complicated procedure may have partially influenced the results.

Our own data were collected under circumstances wherein apprehension and restlessness were prevented or kept at a minimum. The results clearly indicate that under such circumstances, in "normal" subjects and in those with enlarged left ventricles not in failure, GFR, ERBF, and FF are not altered, despite a significant decrease in arterial pressure. This results in a significant reduction in calculated total RVR, and would imply a concomitant decrease in resistance at both afferent and efferent glomerular arteriolar levels.

The results differed strikingly in the patients of Group D, who were in left ventricular failure. The initial average ERBF and GFR were lower than in the other three groups, as would be expected.[11] In these subjects the addition of a heat stress significantly depressed ERBF and GFR further, although in terms of actual volume flow the average changes were small indeed (−8.9 and −13.9 per cent, respectively). Since FF remained unchanged, the most likely assumption is

Table III. *Individual determinations for 10 subjects with enlarged left ventricles and normal wedge pressures (procedure as for subjects in Table II)*

Patient *Age*	*Race, Sex, B.S.*	*Diagnosis*		*Heart rate*	*PBA*	*ERBF*	*GFR*	*FF*	*RVR*
M.B.	N, F	HCVD	C	70	239/128 (170)	568	65	21	301
46	1 57		2 hr.	81	204/120 (151)	697	68	18	.217
S D.	N, F	HCVD	C	68	231/114 (152)	883	100	22	.172
46	1 69		2 hr.	73	206/102 (135)	897	114	24	.151
A.B.	N, F	HCVD	C	62	186/97 (131)	815	95	19	.160
41	1 68		2 hr.	70	179/97 (127)	828	96	18	.150
L.R.	N, F*	HCVD, labile; chronic	C	60	138/70 (95)	247	23	16	385
52	1 52	pyelonephritis	2 hr	67	129/65 (91)	245	26	17	.371
B.A.	N, F	HCVD	C	68	207/128 (159)	590	94	25	.269
41	1.73		2 hr.	74	182/117 (143)	567	90	25	.252
S.H.	N, F	Systolic hypertension; relative	C	83	225/81 (136)	357	59	28	.381
64	1.58	aortic insufficiency	2 hr.	94	216/81 (129)	416	65	26	.310
T.T.	N, F	HCVD	C	75	205/120 (151)	692	87	19	218
47	1.52		2 hr.	86	191/109 (139)	688	81	18	.202
M.F.	N, F	Coronary artery disease	C	57	143/73 (97)	792	75	19	.122
60	1.63		2 hr.	63	132/71 (90)	748	73	20	.120
R.L.	N, F	HCVD	C	61	172/89 (122)	729	84	19	.167
58	1 53		2 hr.	68	155/83 (111)	676	78	19	.164
S.M.	N, M	Coronary disease	C	50	146/88 (113)	925	107	20	122
44	1 82		2 hr.	54	126/79 (101)	862	99	20	117

*Blood urea nitrogen 46 mg. per cent
For key to abbreviations, see footnotes to Table I.

Table II. Individual data for 10 subjects with normal hearts

Patient *Age*	*Race, Sex, B.S.*	*Diagnosis*		*Heart rate*	*PBA*	*ERBF*	*GFR*	*FF*	*RVR*
M.W.	N, F	Idiopathic epilepsy	C*	64	121/79 (97)	882	99	18	.110
36	1 52		2 hr.	78	111/76 (85)	765	106	22	.111
V.E.	N, F	Ganglion left wrist	C	80	138/86 (108)	1,345	128	16	080
27	1.60		2 hr.	83	131/84 (103)	1,740	146	14	.059
M.W.	N, F	Multiple sclerosis	C	52	123/72 (91)	824	99	21	.110
46	1 89		2 hr.	56	118/66 (84)	796	108	23	.105
D.S.	N, F	Pneumonia, left lower lobe; resolved	C	58	163/83 (116)	677	83	19	.171
44	1 60		2 hr.	72	125/67 (93)	724	87	18	.128
C B.	N, F	Systolic hypertension, normal heart	C	81	181/89 (131)	547	84	22	.239
52	1 53		2 hr.	83	141/68 (96)	487	68	19	.197
V.W.	N, F	Erythema nodosum	C	73	125/73 (94)	984	114	18	096
28	1.71		2 hr.	88	97/55 (71)	1,797	114	10	040
E.L.	N, F	Labile hypertension, normal heart	C	78	154/100 (123)	1,138	100	16	.108
38	1 84		2 hr.	84	119/82 (101)	992	107	19	.102
J.K.	W, F	Duodenal ulcer	C	71	103/60 (80)	725	87	21	110
49	1 71		2 hr.	83	99/56 (71)	665	88	23	107
P.C.	N, F	Acute pyelonephritis, treated	C	78	148/97 (119)	619	115	27	192
30	1 71		2 hr.	92	134/88 (107)	578	85	21	.185
R G.	W, F	Bronchopneumonia; resolved	C	73	127/73 (95)	564	80	24	168
35	1 68		2 hr.	78	126/72 (94)	559	76	23	.168

*Initial determinations (C) obtained at 73°F and 40 per cent humidity. Experimental determinations (2 hr) after 2 hours of exposure to 98°F and 40 per cent humidity.
For key to abbreviations, see footnotes to Table I.

the patients who were in left ventricular failure. Indeed, increases were noted in Patients W.Y., L.H., H.B., and R.T. (Table IV). The increase in RVR in these patients seemed to parallel the failure of the arterial blood pressure to decrease in the face of a significant fall in the group as a whole. These 4 subjects likewise were in *combined* right and left ventricular failure at the time of study.

Discussion

The effects of an acute short-term environmental heat stress on renal clearance rates in man which have been reported previously by others show variable results.

Byfield and associates[7] found that exposure to dry heat similar in degree (99.5°F. dry bulb, 19 per cent relative humidity) and duration to the design in the present experiments had no effect on GFR and produced no change in ERPF, except for slight reduction of the latter in patients with chronic glomerulonephritis.

Radigan and Robinson[14] studied healthy volunteers and concluded that a hot, dry environment decreased GFR and ERPF. These experiments were later repeated by Smith, Robinson and Pearcey,[17] who demonstrated that, under the same experimental conditions, clearances decreased only when the test subjects became markedly dehydrated. Water balance was maintained in our experiments by administration of fluid sufficient to obviate an increase in the hematocrit level.

Haapanen[10] studied 20 healthy individuals in a hot (50 to 84°C.) Finnish sauna bath. Clearances of inulin and para-aminohippurate decreased signifi-

Table V. Averages, percentile changes, and significance analyses for the four groups

		Heart rate	PBA	ERBF	GFR	FF	RVR
A. Controls	C	75	(97)	666	79	20	.166
	2 hr.	75 0%	(104) +7.2%	664 0%	79 0%	20 0%	.176 +6%
	p (C vs 2)	—	< 005 > 001	> .1	—	—	< .2 > .1
B. Normal heart, heat	C	71	(105)	830	100	20	.138
	2 hr.	80 +12 7%	(90) −14 3%	910 +9.6%	98 −2%	19 −5%	.120 −13%
	p (C vs 2)	< .005 > .001	< .005 > .001	< 5 > 4	< 7 > .6	< .5 > .4	> .001
C. Enlarged left ventricle, normal wedge pressure, heat	C	65	(133)	660	79	21	.230
	2 hr.	73 +10 9%	(122) −8.2%	663 +0.4%	79 0%	21 0%	.205 −10.9%
	p (C vs 2)	> 001	> .001	< .9 > .8	—	< .6 > .5	> .001
D. Enlarged left ventricle, elevated wedge pressure, heat	C	67	(140)	533	72	25	.330
	2 hr	73 +9%	(126) −10%	485 −8 9%	62 −13.9%	23 —	.328 −0.6%
	p (C vs 2)	< .005 > .001	< .005 > .01	< 001 > .005	> .001	< .3 > .2	< .9 > .8

Significance analyses of Control Group A versus Groups B, C, and D. The comparisons are between the final percentile changes in Group A versus those in the other groups (Fisher's "t" test, groups less than 30)

	Heart rate	PBA	ERBF	GFR	FF	RVR
p (Controls vs B)	< .05 > 02	< .001 > 005	< 9 > .8	< .8 > .7	< .7 > 6	< .05 > .02
p (Controls vs C)	< .02 > 01	> .001	< .9 > .8	< .8 > .7	< .9 > .8	> .001
p (Controls vs D)	< 02 > 05	< 005 > .01	< .2 > .1	< .02 > .01	< .3 > .2	< .6 > .5

For key to abbreviations, see footnotes to Table I.

Table IV. Individual determinations for 10 subjects with enlarged left ventricles and elevated wedge pressures (procedure as for subjects in Tables II and III)

Patient Age	Race, Sex, B.S.	Diagnosis		Heart rate	PBA	ERBF	GFR	FF	RVR
W.Y.	N, M*	Syphilitic aortic insufficiency	C	68	168/60 (97)	660	65	18	.147
63	1 70		2 hr.	74	163/62 (96)	508	54	19	.189
R.Y.	N, F	HCVD	C	66	222/120 (157)	815	112	22	.193
40	1 63		2 hr.	70	194/107 (138)	802	96	19	.172
M.L.	N, F	Coronary artery disease; HCVD	C	63	190/89 (126)	766	83	21	.164
60	1 47		2 hr.	75	149/78 (103)	657	69	20	.157
S.J.	N, F	HCVD	C	76	205/122 (159)	522	78	27	.305
55	1.60		2 hr.	80	179/80 (119)	479	61	23	.248
L.H.	N, M†	Coronary artery disease; chronic pyelonephritis	C	61	128/65 (85)	279	30	16	.305
68	1.70		2 hr.	72	126/67 (85)	226	24	16	.376
H.B.	N, M‡	HCVD	C	59	252/109 (157)	462	67	31	.340
58	1.74		2 hr.	59	249/107 (152)	445	66	32	.342
V.T.	N, F§	HCVD	C	66	229/111 (159)	306	63	31	.520
35	1.64		2 hr.	74	206/100 (140)	297	62	31	.471
R.T.	N, F‖	HCVD; chronic pyelonephritis	C	86	247/125 (174)	198	45	35	.879
45	1 76		2 hr.	86	247/123 (172)	193	37	30	.891
S.L.	N, F	HCVD	C	70	242/132 (173)	578	82	26	.299
54	1 80		2 hr.	80	212/124 (158)	553	63	21	.286
W W	N, M	Coronary artery heart disease	C	57	165/83 (111)	746	95	24	.149
59	1 70		2 hr.	61	150/78 (102)	696	87	23	.147

For key to abbreviations, see footnotes to Table I.

*Pressure in right ventricle 36/9 mm Hg; recent recovery from severe failure on right side; venous pressure still slightly elevated (14.5 cm. of saline).

†Pressure in right ventricle 48/16 mm Hg; blood urea nitrogen 35 mg. per cent.

‡Pressure in right ventricle 46/14 mm. Hg

§Recently in severe failure on right side; venous pressure 12 cm. of saline; pressure in right ventricle 34/7 mm. Hg at time of study.

‖Pressure in right ventricle 51/12 mm. Hg; venous pressure 16 cm. of water; blood urea nitrogen 23 mg per cent.

the occurrence of afferent arteriolar constriction. The reason for this is not apparent.

It is also of interest in this group of subjects that the 4 individuals who were in *combined* ventricular failure shared an increase in RVR coupled with a failure of the arterial pressure to fall. There was, however, no direct relation between these events and the degree of fall in ERBF and GFR. The number of patients studied is not sufficiently large for a comparison among patients with simple left and concomitant right-sided failure, but the effect of heat on the renal clearances of the latter merits further investigation.

That a diversion of blood from the kidneys takes place in patients with left ventricular failure when these subjects are exposed to a hot environment is evident. Despite the fact that in a short-term exposure the amounts seem small, on the average, it is difficult to escape the suggestion that the impaired renal function of patients in heart failure could be further aggravated by a hot environment, thus compounding over a longer period of time the deleterious effects of an already reduced renal blood flow upon the state of cardiac compensation.

The universal air-conditioning of hospital rooms is an important measure for

Case report

Right atrial myxoma. Report of a case and review of the literature

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Primary cardiac neoplasms are rare, appearing in 0.05 per cent of unselected autopsies.[1] Nevertheless, they are worthy of consideration since open-heart surgery makes their successful removal possible. Because these tumors grow in otherwise normal hearts, there is the unique opportunity of completely curing patients who show grave heart symptoms. Kirkeby and Leren[2] and Goldberg and co-workers[3] were the first to diagnose intracardiac myxomas during life (in both cases the tumors were on the left side). Since Crafoord[4] described the first successful operation on a patient with a myxoma in the left atrium, a gradually increasing number of reports has been made of patients with myxomas in the left and right atria who have undergone operation.

The case of a patient with a myxoma in the right atrium is presented here, together with some comments upon the symptomatology and results reported in 20 other patients with myxomas in the right atrium who were operated upon[5-24]; in 15 of these 20 the diagnosis was made preoperatively, and 11 survived the operation and the immediate postoperative course (Table II).

Case report

The patient was a 56-year-old farmer's wife who had no history of previous rheumatic disease. She had been healthy until 2 years ago, when dyspnea and tachycardia upon exertion appeared. One year ago, edema of the legs occurred for the first time. During the last 6 months these symptoms progressed so far that she was unable to do her housework. Marked peripheral cyanosis with cold hands and feet was also apparent at that time. The liver was moderately enlarged, with no signs of ascites. Arteriography of the lower extremities, which was carried out because peripheral vascular disease was suspected, gave normal findings. There was no history of chest pain, flushing or fainting, and the lungs were normal on physical and roentgenographic examination. She was symptomatically treated with digitalis, saluretics, and vasodilators, but with only moderate effect.

After preliminary investigation, she was admitted to Sahlgren's Hospital under the tentative diagnoses of either (1) constrictive pericarditis localized to the right side of the heart, or (2) obstruction to blood flow through the tricuspid ostium due to an endocardial myxoma or a carcinoid tumor. These possibilities were suggested by the clinical history, together with signs of congestion in the systemic circulation and enlargement of the liver in the absence of any signs of pulmonary congestion.

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the general well being of patients in geographic areas in which prolonged periods of warm or hot weather, dry or humid, are prevalent. It may not always be financially feasible, nor necessarily practical, in locations in which such weather may be expected to occur only a few days at a time during scattered intervals in the summer months. However, this study further points up the need[4,5] for a number of suitably air-conditioned units for at least the temporary handling of patients during critical periods of cardiac decompensation. The indications for similar preferential treatment of patients with severe chronic pulmonary emphysema have already been presented.[19]

Summary

Renal clearances of mannitol (GFR) and para-aminohippurate (ERBF) were determined in patients with normal hearts, with enlarged left ventricles not in failure, and with enlarged left ventricles in failure, before and after a resting exposure for 2 hours to a warm and dry environment of 98°F. and a humidity of 40 per cent.

GFR and ERBF did not change, and renal vascular resistance decreased in the first two groups of subjects. In the patients who were in left ventricular failure, significant decreases occurred in GFR and ERBF, whereas renal vascular resistance, on the average, remained unchanged; the latter actually increased in those patients who were in combined failure at the time of study.

The need for suitable air conditioning for these patients is emphasized.

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Fig. *2*. Angiocardiogram (present case) at point *A* in Fig. 1; the tumor is situated in the right atrium.



Fig. *3*. Angiocardiogram (present case) at point *B* in Fig. 1; the tumor is midway between the right atrium and the right ventricle, occluding the tricuspid orifice.

now was entered from the right saphenous vein, was performed. On fluoroscopy it was noticed that, when passing the atrium, the catheter looped downward in a strange way before entering the right ventricle. Angiocardiography gave complete evidence of a movable tumor, the size of an orange, in the right atrium; the tumor was pressed down into the right ventricle during diastole, and then was pushed back into the atrium again during ventricular systole. The right atrium was only moderately enlarged.

An angiocardiogram, with six pictures per second, was taken and each picture produced a marking on the simultaneously recorded ECG tracing. This made possible a detailed analysis of the relationship between the fluctuations in the right atrial pressure recording and the corresponding displacement of the tumor mass within the right atrium and the right ventricle. The right atrial pressure curve (Fig. 1) was recorded through an angiocatheter immediately before injection of contrast into the right atrium.

The right ventricle was filled with contrast medium mainly during the early phase of rapid filling (Fig. 2). Contrast medium surrounded the tumor



Fig. *4* Angiocardiogram (present case) at point *C* in Fig. 1; the tumor is pushed far down into the right ventricle during atrial systole.



Fig. *5*. Angiocardiogram (present case) at point *D* in Fig. 1; the tumor is situated in the right atrium at its greatest distance from the tricuspid valve.

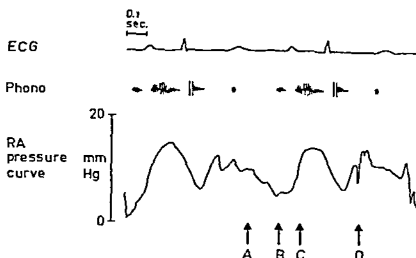


Fig. 1. Right atrial (RA) pressure curve in the present case. The letters A-D refer to corresponding pictures of the angiocardiogram (Figs. 2-5).

At the time of admission (May 18, 1961) she had moderate edema of the legs and pronounced peripheral cyanosis, especially of her toes, and her hands and feet were cold. There was no dyspnea at rest. The neck veins were distended, and a distinct presystolic wave was visible in the venous pulse. Neither the apex beat nor precordial pulsations were palpable. From the preliminary auscultatory findings it was stated that she had a regular gallop rhythm with a loud third sound, which on the phonocardiogram appeared as a murmur during atrial systole. A systolic murmur, Grade 3, was heard in the fifth intercostal space immediately to the left of the sternal border; this murmur was markedly accentuated during inspiration but did not change with the position of the patient. The blood pressure was 110/75 mm. Hg in both arms. The liver was not palpable. Her temperature at the time of her admission to the hospital, and subsequently, was slightly elevated to about 38°C.

Laboratory tests showed a red blood cell count of 5.6 million per cubic millimeter, with a hematocrit of 50 per cent and a hemoglobin content of 17.3 Gm. per cent. Blood sedimentation rate was 2 mm. per hour. Slight albuminuria was intermittently present, and serum creatinine was in the upper range of normal (1.5 mg. per cent). Liver tests were pathological, with bilirubin in serum 2.4 mg. per cent, alkaline phosphatases 11 units, and a Bromsulphalein retention of 25 per cent in 30 minutes. Thymol test and transaminases (GOT and GPT) were normal.

The ECG showed a sinus rhythm with a pathologic P-Q time of 0.32 second and ventricular extrasystoles. The electrical axis was normal. The P waves in Leads V_{1-4} were high, which suggested hypertrophy of the right atrium. The QRS complexes were very low and distinctly abnormal in Leads $V_{1,2}$. Changes in the S-T segments were probably due to previous digitalis therapy, which also might explain the prolonged conduction time.

Roentgenographic examination of the heart gave a relative heart volume of 360 ml. per square meter of body surface area. The size and configuration of the heart, the great vessels, and the peripheral lung vessels were interpreted as being normal.

Catheterization of the right side of the heart via the left arm was performed. The catheter was passed into the pulmonary artery without difficulty or unusual distortion. The most obvious finding was a clear-cut diastolic gradient over the tricuspid valve (Table I). Cardiac output, determined by means of the dye-dilution technique, was very low—2.4 L. per minute.

The diastolic gradient over the tricuspid valve strengthened the suspicion of an obstructive lesion, and angiocardiography from the right atrium, which

Table I. Right heart catheterization findings in the present case

Right atrial pressure	15/4 (mean = 10) mm. Hg
Right ventricular pressure	16/−1 mm. Hg
Pulmonary arterial pressure	15/4 (mean = 8) mm. Hg
Cardiac output	2.4 L./min.
Cardiac index	1.6 L./min./M.² body surface area
Stroke volume	37 ml./beat
Oxygen saturation in the pulmonary artery	58.2 per cent
Oxygen saturation in the brachial artery	97.0 per cent
Arteriovenous oxygen difference	74 ml. of oxygen per liter of blood
Oxygen consumption at rest	172 ml./min.

right atrium who were operated on

ECG	*Radiography and/or fluoroscopy*	*Catheterization results*	*Size and weight of tumor*	*Comments*	*Results*
—	Fluoroscopy normal	RA 18/3(12); RV 18/0 CI 1.34	—	Only partial resection of tumor§	Died after 24 days; gastric dilatation and electrolyte disturbances
Right bundle branch block RA and RV hypertrophy	Hypertrophy of RA and RV	RA 13; RV 8	—	Attacks of paroxysmal dyspnea with cyanosis when bending forward§	Died postoperatively
—	Normal	—	—	Combined with atrial septal defect and right-to-left shunt§	Living after 2 wk.
Supraventricular extrasystoles. Nonspecific T-wave changes	Some right heart enlargement. Lung fields normal	RA 3.5, RV 17/2 SaO_2 PA 45% SaO_2 BA 81%	Approx. 13×14 cm.	Varying oxygen saturation with body position. Interatrial septal defect†	Living after 6 mo. Easily tired; otherwise normal
Fast, impure auricular flutter	Cardiomegaly; possibly RA enlargement	RA 24-30 (at operation)	Approx. 10×9 5 cm. 175 Gm.	Tricuspid insufficiency Grade 2 at operation†	Living after 4½ mo. without troubles
Right bundle branch block and ventricular overload	RV enlargement. Small aorta and pulmonary artery. Visible tumor at fluoroscopy	—	4.5×5×5.5 cm. 49.8 Gm.	‡	Discharged with signs of remaining tricuspid insufficiency
Tendency to right axis deviation. RA hypertrophy	Cardiomegaly Lung fields strikingly free of vascular engorgement	Mean pressure gradient between RA and RV 26 mm. Hg	9×8.5×5 5 cm.	Large giant A wave in distended neck veins†	Died on the operating table in ventricular fibrillation
Low voltage in right precordial leads. RA hypertrophy	Slight RA and RV enlargement. Pulmonary artery and pulmonary vasculature diminished	RA 12/7(10); RV 17/3 CI 1.9 SaO_2 PA 49 2% SaO_2 BA 86.6%	—	Presystolic pulsations in neck veins‡	Hemiplegia on right side. Died after 24 hr.

blood cell count (million/cu. mm). ESR: Erythrocyte sedimentation rate (mm /1 hr) RA. Right atrium (pressure in mm Hg) RV: SaO_2 PA: Oxygen saturation in pulmonary artery. SaO_2 BA (or FA): Oxygen saturation in brachial (or femoral) artery.

Table II. Collected data from case records in the literature on patients with myxomas in the

Author(s)	*Patient sex, age*	*Preliminary diagnoses*	*Duration of symptoms (mo.)*	*Means of obtaining definite diagnosis*	*Auscultatory findings*	*BP and VP*	*Hgb, RBC, Hct, and ESR*
Bahnson and Newman[5]* (1953)	F, 54	1. Nephrosis 2. Cardiac compression 3. Constrictive pericarditis	78	Angiocardiography	Systolic and diastolic murmur (earlier a presystolic murmur)	BP 95/70 VP 17-19.5	HCT 57-63%
Paquet[7] (1956)	M, 39	—	—	Angiocardiography	—	BP 120/80-100/60 VP 26-33-23	—
Hanlon[8] (1957)	F, 61	—	60	Angiocardiography	—	—	—
Coates and Drake[9]*** (1958)	F, 50	1. Alveolocapillary block syndrome 2. Subacute bacterial endocarditis 3. Severe anemia	6	Angiocardiography	Systolic murmur, third sound and protodiastolic gallop, varying from time to time	BP 110/70	Hgb 11.5 ESR 38
Ellis, et al.[10]**** (1958)	M, 48	1. Constrictive pericarditis 2. Tricuspid stenosis	17	At operation for tricuspid stenosis	Four heart sounds at apex (gallop sound). Systolic murmur. To-and-fro friction rub	BP 90/60	Hgb normal ESR 38
Krčilková, et al[12] (1958)	F, 14	Rheumatic carditis	96	Fluoroscopy	Indistinct heart sounds. Systolic murmur, varying with position	BP 115/80	—
Lyons, et al.[13] (1958)	M, 51	—	5	Angiocardiography	Loud presystolic murmur, with marked respiratory variations and a late diastolic murmur	—	—
Belle[14] (1959)	F, 43	1. Tricuspid stenosis 2. Ebstein's anomaly	11	Angiocardiography	Presystolic murmur, increasing during inspiration; third heart sound	BP 90/72	Blood counts normal

*Also reported by Bahnson and co-workers.[6] **Also reported by Taber and Lam.[21] ***Also reported by Campeau and David[11]
†Operated on with extracorporeal circulation. ‡Operated on in hypothermia. §Method used not reported.
BP: Arterial blood pressure (mm. Hg). VP: Venous blood pressure (cm. H_2O). Hgb: Hemoglobin content (Gm./100 ml.) RBC: Red
Right ventricle (pressure in mm. Hg). CO: Cardiac output (L./min.). CI: Cardiac index (L./min./M² body surface area).

in the right atrium who were operated on

ECG	Radiography and/or fluoroscopy	Catheterization results	Size and weight of tumor	Comments	Results
Right axis deviation. Low voltage in all leads	RA and RV enlargement. Inconspicuous pulmonary artery	RA 19/17(15); RV 10/0	Approx. 13.5×13.5 cm.	§	Died on the operating table. Pulmonary embolism of tumor fragments
Extremely low voltage of all cardiac complexes. RA enlargement	Moderate cardiac enlargement. Pulmonary congestion. Bilateral pleural effusion	RA 22; RV 15/5 CI 1.24	—	Circuitous course of the catheter in reaching RV†	Living after 6 mo. Almost complete relief of symptoms
RA and RV hypertrophy	Fluoroscopy normal	RA 15/8(10); RV 17/8	8×7×3 cm.	Emboli to the lungs 48 hr. after operation†	Died suddenly after 24 days
Impression of myocardial ischemia or myocarditis	Normal	RA 18/8; RV 20/4	9×4 cm. 100 Gm.	Dizziness when lying on the right side‡	Living after 1 mo., without symptoms
RA and RV hypertrophy	RA enlargement. Pulmonary vasculature diminished	Marked gradient between RA and RV	6×4 5 cm.	‡	Living without symptoms after 12 mo.
Peaked P waves in Leads II and aVr. Low T waves in precordial leads	Normal	—	6 cm in diameter	Frequent attacks of dizziness, flushing and perspiration†	Discharged in excellent condition
Low voltage and prominent P waves	Enlargement of RA and RV. Pulmonary vasculature normal	Diastolic gradient between RA and RV. Low cardiac output	—	†	Died
Low voltage and prominent P waves	Enlargement of RA and RV. Pulmonary vasculature normal	Diastolic gradient between RA and RV. Low cardiac output	—	†	Said to be well
RA hypertrophy. Peaked T waves	Normal	RA 20/5; RV 27-45 systolic. End-diastolic pressure gradient 15	10×8×4 cm.	†	Living after 6 mo., without symptoms

Table II—Cont'd. *Collected data from case records in the literature on patients with myxomas*

Author(s)	*Patient sex, age*	*Preliminary diagnoses*	*Duration of symptoms (mo.)*	*Means of obtaining definite diagnosis*	*Auscultatory findings*	*BP and VP*	*Hgb, RBC, Hct, and ESR*
Cooley, et al.[15] (1959)	F, 43	Constrictive pericarditis	—	At operation for constrictive pericarditis	Normal	BP 100/80 VP elevated	—
Cooley, et al.[15] (1959)	F, 48	—	12	Right heart catheterization	Normal	BP 90/75 VP 30	—
Mathey, et al[16] (1959)	F, 25	Pericarditis	48	Angiocardiography	Split second sound. Mesodiastolic murmur. To-and-fro friction rub	BP 105/80 VP 21	—
Padhi, et al.[17] (1959)	M, 46	1. Tricuspid stenosis 2. Constrictive heart disease	18	Angiocardiography	Systolic murmur. Changing diastolic murmur	BP 120/95	Hgb 14.2 HCT 47% ESR 27
Alessandri, et al[18] (1960)	F, 52	1. Constrictive pericarditis 2. Tricuspid stenosis	8	At operation	Diastolic murmur with presystolic accent, increasing during inspiration	BP 135/100 VP 25	Hgb 20.5 HCT 57% ESR 4
Ashman, et al.[19] (1960)	M, 38	Carcinoid tumor	3/4	Angiocardiography	Normal (later, murmurs varying with position appeared)	BP 110/70 VP 13 5	Hgb 14.9 RBC 4.91 HCT 47%
Campeti, et al.[20] (1960)	—	—	—	Cineangiocardiogram	Loud diastolic murmur	—	Markedly elevated ESR
Campeti, et al.[20] (1960)	—	—	—	Cineangiocardiogram	Loud diastolic murmur	—	Markedly elevated ESR
Taber and Lam[21] (1960)	F, 54	Carcinoid tumor	72	At operation for (1) tricuspid stenosis or (2) right atrial tumor	Systolic and mid-diastolic murmur, changing from time to time	BP 120/80 VP 26	—

in the right atrium who were operated on

ECG	Radiography and/or fluoroscopy	Catheterization results	Size and weight of tumor	Comments	Results
RA hypertrophy	—	RA 14/6(9); RV 20/2(10) CO 3 8 SaO_2 PA 69% SaO_2 FA 96%	—	§	Died 3 hr. after operation
Low voltage. Right bundle branch block. Large P waves	RA and RV enlargement. Fluid at base of right lung (due to tumor emboli?)	RA 23/13(15); RV 15/5	8×6×4.5 cm.	Prominent A wave in neck veins†	Died after 48 hr.
Low voltage. RA hypertrophy	Enlargement of RA and possibly RV. Slightly decreased vasculature in lungs	SaO_2 BA 93%	8 cm. in diameter 247 Gm.	Tricuspid insufficiency at operation†	Living after 10 mo, completely asymptomatic
Low voltage RA hypertrophy. Prolonged P-Q time and ventricular extrasystoles	Normal	RA 15/4(10), RV 16/-1 CI 1 6 SaO_2 PA 58.2% SaO_2 BA 97%	7×4×3 5 cm. 100 Gm.	Prominent A wave in neck veins. Moderate tricuspid insufficiency at operation†	Discharged without symptoms

intensity very markedly during inspiration and was interpreted as a sign of slight tricuspid insufficiency. The neck veins were no longer distended The serum bilirubin became normal, and Bromsulphalein was now retained to only 10 per cent in 30 minutes. She was sent home in good condition on June 30, 1961. When last seen about 7 months later, she was almost free from subjective symptoms, except for slight dyspnea upon exertion.

Comments

Myxomas are said to be the most common, or comprise about half, of all primary cardiac tumors; they have been found within a wide age range of patients, from 3 months to 68 years.[24] They appear three times more frequently in females than in males.[10,15] Most of them are situated in the left atrium, and only about a fourth in the right atrium, where, as a rule, they are attached by a pedicle to the septal wall in the region of the fossa ovalis.[24] There has been much discussion among pathologists as to whether these tumors are true neoplasms or old, organized thrombi. Prichard,[26] among others, however, considers them to be true neoplasms.

In Tables II and III the symptomatology and other pertinent data from the previously reported and the present cases of right atrial myxomas diagnosed and operated upon in vivo have been assembled, in so far as it has been possible to ascertain these data from the case histories quoted. Twelve of the patients were females and 7 were males, and their ages ranged from 14 to 61 years, with 14 subjects between 35 and 55 years old.

The duration of symptoms has often been short, and in 10 patients was 2 years or less. According to their histories, the patients were almost always free from rheumatic fever or repeated tonsillitis. The most common complaint reported in 14 patients was dyspnea upon exertion. Fainting, possibly due to temporary obstruction of the blood flow, occurred in 5 patients, characteristically with changes

Table II—Cont'd. *Collected data from case records in the literature on patients with myxomas*

Author(s)	*Patient sex, age*	*Preliminary diagnoses*	*Duration of symptoms (mo.)*	*Means of obtaining definite diagnosis*	*Auscultatory findings*	*BP and VP*	*Hgb, RBC, Hct, and ESR*
Turski, et al.[22] (1960)	F, 45	Combined tricuspid stenosis and insufficiency	—	At operation for tricuspid disease	Systolic and presystolic murmur	BP 120/85 VP 16	—
Adams, et al.[23] (1961)	M, 33	Acute nonspecific pericarditis	15	Angiocardiography	Prominent third sound. Holodiastolic murmur, varying with position and respiration	BP 100/76 VP 32	Hgb 15.7 HCT 50%
Levinson and Kincaid[24] (1961)	M, 37	Polycythemia vera	57	Angiocardiography	Normal	VP 21	Hgb 20.3 RBC 6.05 HCT 65%
Own case (1961)	F, 56	1. Constrictive pericarditis 2. Tricuspid obstruction by myxoma or carcinoid tumor	24	Angiocardiography	Systolic and presystolic murmur, increasing during inspiration	BP 110/75	Hgb 17.3 RBC 5.6 HCT 50% ESR 2

and reached the right ventricle. During this phase the tumor was pushed toward the tricuspid valve, intermittently occluding the orifice. The corresponding part of the right atrial pressure recording showed irregular pressure oscillations.

The pressure then dropped slowly. Immediately before atrial contraction the tumor was pushed midway between the right atrium and the right ventricle. The orifice was more or less totally occluded (Fig. 3). Approximately at this time a third sound (or murmur) was recorded in the phonocardiogram. During atrial systole the pressure increased rapidly to a high level, and the tumor was pushed far down into the right ventricle (Fig. 4). A presystolic murmur was recorded, with its maximum at the highest point of the atrial pressure wave.

During ventricular systole the tumor was rapidly pressed back into the right atrium again. Approximately at the end of the phase of rapid ejection the tumor was completely in the right atrium at its greatest distance from the tricuspid valve (Fig. 5). During the phase of rapid ejection there was a double-peaked rise in right atrial pressure; the first peak might have been due to the rapid displacement of the tumor from the ventricle to the atrium, whereas the second peak might have indicated regurgitation of blood during ventricular systole.

Operation was performed on June 13, 1961. A right anterior thoracotomy was made, extending to the sternum, which was divided. No thrill was palpable over the chambers of the heart or great vessels, but the inferior caval vein was found to be markedly dilated. The patient was connected to the Crafoord-Senning-AGA heart-lung machine[25] and bypass started. The right atrium was opened widely, and the big tumor was seen to be almost plugging the tricuspid orifice. The tumor had a smooth surface covered by endocardium, and it felt rather soft. The base of the tumor appeared to be adherent to the atrial septum at the fossal region in an area of about 2 sq. cm. Examination of the tricuspid leaflets did not reveal any abnormalities, except slight dilatation of the valvular ring. The total perfusion time was 27 minutes, and the heart contractions were immediately strong and regular.

The excised tumor measured 7 by 4 by 3.5 cm. and weighed 100 grams (Fig. 6). The tumor had a brittle consistency, and the cut surface was grayish-white and semitranslucent. Histologic examination showed the typical picture of a myxoma without any signs of infiltrative growth.

The postoperative course was uneventful, except for a transient complete atrioventricular block the day after operation. The peripheral cyanosis disappeared, and the patient's previous dyspnea improved. On auscultation a systolic murmur, Grade 3, was now heard at the left sternal border in the fourth to fifth intercostal space. It increased in

neck veins, which usually are distended. The classic sign of murmurs which change character with the position of the patient has been reported in only a couple of cases. Characteristically, the arterial blood pressure was low, and the venous blood pressure was elevated.

The electrocardiogram was pathologic in all subjects but one of those commented upon. Low voltage and signs of right atrial hypertrophy with high peaked P waves in the right precordial leads seem to be a rather constant pattern.

Radiography and/or fluoroscopy were not very satisfactory, and gave normal findings in 7 cases. The most frequent findings seem to be pulsation of wide caval veins, right atrial enlargement, and, as an important indication, a small pulmonary artery and a diminished vasculature in the lungs. These findings, however, are identical with those in tricuspid valvular disease of other origin. Embolization of parts of the tumor may give rise to a picture of pulmonary infarction.

The right atrial pressure was elevated in all but one of the cases in which it was reported; often the elevation was very marked, up to 20 to 30 mm. Hg. Characteristically, there were a high A wave and a diastolic gradient over the tricuspid valve. The shape of the curves was sometimes said to be consistent with a tricuspid stenosis and/or insufficiency.

The right atrial pressure tracing in the present case differs distinctly from a normal right atrial pressure curve and from the pressure curve of tricuspid stenosis (Fig. 7). In the present case the main characteristics of the tracings recorded on two different occasions are: (1) marked irregularity of the curve contour during the phase of rapid filling, due to intermittent occlusion of the tricuspid orifice; (2) high pressure wave during atrial contraction because of momentary total occlusion of the tricuspid orifice when the tumor is midway between the right atrium and the right ventricle; and (3) marked increase in pressure covering the whole of ventricular systole, with absence of a normally present dip. The latter is due to regurgitation of the tumor and of blood; this is supported by the findings at operation, at which time a slight dilatation of the valvular ring and a systolic jet were felt.

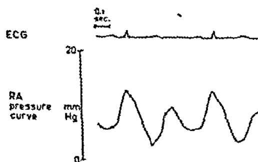


Fig. 7. Right atrial (*RA*) pressure curve in a case of valvular tricuspid stenosis.

Whether this pattern of the right atrial pressure curve is a constant finding is difficult to evaluate from the published pressure curves,[5, 11, 12, 14, 15] wherein some confusion exists as to the lowest pressure point in the curves.

Our findings indicate that the most significant deviations from the normal or tricuspid stenosis pressure curve which suggest a myxoma are to be sought during the phase of rapid filling. The absence of a dip during ventricular systole also seems to be an important sign. No conclusive statements can be made, however, because the interference of the tumor with normal hemodynamics depends on its size. The excised tumors have always been relatively big; the smallest one reported measured 4.5 by 5 by 5.5 cm.[12] It seems that the tumor must be of a certain size before it is capable of interfering with heart action.

Of the 21 patients who were operated on, 19 survived the operation, and 2 died on the operating table. Seven patients died during the postoperative course. Twelve patients could be sent home, and 9 of these are stated to be asymptomatic and in excellent condition. The longest follow-up reported is 1 year.

Summary

Right atrial myxomas are rare tumors, but should be suspected in patients, especially women 35 to 55 years old, who have a relatively short history of progressing right heart failure, cyanosis, weakness and, sometimes, pulmonary embolism,



Fig. 6. Present case. The cut surface of the tumor, which measured 7 by 4 by 3.5 cm.

in body position. Seven patients were said to be frankly cyanotic, apparently because of low cardiac output and diminished peripheral blood flow. Almost every one presented some sign of right heart failure, which had responded little or not at all to digitalis therapy. The histories showed that the patients had been remarkably free from embolic episodes, which otherwise are said to be a typical feature in the symptomatology of this tumor, because part of it breaks off and is carried away by the blood stream.

The correct diagnosis was not reached immediately in any subject, and the various preliminary diagnoses attempted are shown in Table II. Most commonly, pericarditis, with or without constriction, was suspected; this was the preliminary diagnosis in 8 patients. Twice the preliminary diagnosis was carcinoid tumor because of attacks with flushing and perspiration, and in 1 patient in whom such episodes were frequent an abdominal exploration was performed.[19] Recently, Levinson and Kincaid[24] reported 1 case which was at first diagnosed as polycythemia vera; and in 2 other patients, high hematocrit values have been reported. In 5 patients the definite diagnosis was not obtained until operation, which was usually performed because a tricuspid valvular stenosis was suspected. Without doubt, the best way to reach an exact diagnosis is by means of angiocardiography, which revealed the tumor in 14 cases. As in our patients, a circuitous course of the catheter was found once and gave the clue to the diagnosis.[15]

The auscultatory findings were not generally conclusive, and, in fact, in 4 patients they were quite normal. The most characteristic feature seems to be a loud presystolic murmur, which increases markedly during inspiration and is associated with a visibly prominent A wave in the

*Table III. Symptoms and objective findings in 19 patients with myxomas in the right atrium who were operated on**

Symptoms and findings	*Present*	*Not present*	*Not reported*
Dyspnea on exertion	14	1	4
Weakness and easy fatigability	12	–	7
Attacks of fainting with or without cyanosis	5	2	12
Attacks of dyspnea and cyanosis	2	1	16
Precordial pain	4	1	14
Palpitations	3	1	15
Dizziness	3	1	15
Attacks of flushing and perspiration	1	1	17
Cold hands and feet	1	–	18
Fever	3	2	14
Dyspnea at rest	5	5	9
Edema, especially of the lower extremities	12	1	6
Cyanosis	7	4	9
Distended neck veins	14	2	3
Enlargement of the liver	13	1	5
Ascites	4	3	12

*The patients of Hanlon[1] and Turski and associates[22] are not included.

Clinical pathologic conference

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Clinical abstract

A 55-year-old man, a boat builder, was admitted to the Hospital under the care of Dr. Reginald G. Epps on Aug. 26, 1961, in a state of congestive heart failure.

The patient said that he had not felt well since 1957. In that year he had noticed, while traveling abroad, that carrying portmanteaux made his elbows ache. In England, he took medical advice, which was to the effect that he had osteoarthritis of the elbows. For 12 months past he had noticed numbness of all *his fingers, which felt as though gloved, so that he* had difficulty with buttons. Six months previously he had consulted an orthopedic surgeon, who diagnosed cervical spondylosis and applied traction to his neck, without benefit. In recent months he had suffered from lassitude and had become easily fatigued and short of breath on slight exertion. Three months previously he had developed swelling of the ankles. A local doctor had administered vitamin tablets, without relief, but a change to chlorothiazide (250 mg. twice daily) relieved both the swelling of the ankles and the numbness of his fingers. Over the previous 3 months also he had noticed huskiness of his voice and difficulty in swallowing dry foods. All his symptoms had worsened during the 3 or 4 weeks prior to admission. The skin had become tight over his fingers and had begun to crack at the edges of the nails. The tips of the fingers were sore.

Four weeks previously he had awakened one night unable to speak distinctly and had found the left side of his face paralyzed. The local doctor had diagnosed Bell's palsy. Over the next 3 days this trouble had cleared up.

He said that he had felt the cold more than ever before during the current winter, and that he had always preferred the hot seasons. His skin and hair had always been dryish, and he thought that his hair was becoming drier.

He had had no cough, no expectoration, no pain *in the chest, no headache, and no alimentary nor* urinary symptoms.

On examination he looked rather younger than his years and was intelligent and alert, but his face was described as being curiously expressionless. The skin was drawn tightly over the middle and distal phalanges of his fingers, and cracks were present as described. There was no tendency to clubbing of the fingers.

His pulse was regular, and the resting rate was 84 per minute. The right external jugular vein was visibly pulsatile and dilated for 5 inches above the clavicle. There was slight edema of the ankles and legs. The apex beat of the heart was palpable in the fifth left intercostal space 5 inches (12.5 cm.) from the midline. The first heart sound was diminished in loudness and muffled in tone at the apex of the heart; a third sound was audible in mid-diastole; the second

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and no history of rheumatic disease. A presystolic murmur, which varies with respiration, and a dominant A wave in distended neck veins can be found. A low arterial blood pressure, an elevated venous pressure, and a tendency toward polycythemia support the diagnosis, as do signs of right atrial hypertrophy in the electrocardiogram and radiographic evidence of enlargement of the right atrium and reduced vasculature of the lungs. Catheterization of the right side of the heart will show an elevated right atrial pressure and a diastolic pressure gradient over the tricuspid valve, and the course of the catheter may indicate the presence of a tumor. However, angiocardiography is the most reliable means of obtaining an exact diagnosis.

Absence of pulmonary congestion without orthopnea, with a clear picture of congestive failure, conclusively shows that the tumor is situated in the right heart. The main differential diagnoses are valvular tricuspid stenosis, constrictive pericarditis, and carcinoid tumor.

Patients with right atrial myxomas are good candidates for open-heart surgery, using extracorporeal circulation or hypothermia, and a high percentage of them will be cured.

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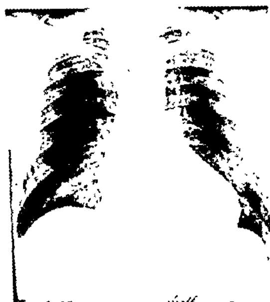


Fig. 1. X-ray film of the chest made on Sept. 4, 1961.

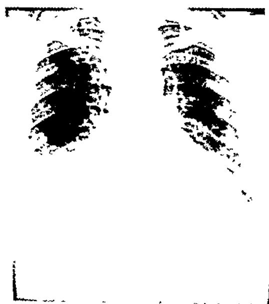


Fig. 2. X-ray film of the chest made on Oct. 27, 1961.

slight degree of increased pigmentation of the hands and, in fact, over the exposed parts of the body. It was not much.

DR. PUPLETT: Thank you. I wish, first, to discuss the heart. For some months this patient had been suffering from shortness of breath. Then we are told that he had raised jugular venous pressure and edema, which suggests right heart failure. In addition, the heart was enlarged transversely, the heart sounds were not of good quality, and there was a third heart sound which, I assume, was heard over both right and left ventricles. Now, I would like to see the x-ray films (Figs. 1-3). Yes, they show that the heart is enlarged. There is no increase in pulmonary vascular markings, and we are told that the left atrium is not enlarged. Next, let me see the electrocardiograms (Fig. 4). The P-R interval is slightly prolonged, greater than 0.2 second, so that at this stage we can say that the patient had right ventricular failure, but that there was diffuse cardiac involvement. Presumably, there was involvement of the left ventricle also, because of the breathlessness; and the electrocardiogram shows depression of the T wave over the left ventricle (in Leads V_5 and V_6), and there is a prolonged P-R interval.

Now we come to the rest of the clinical story in regard to the heart. We see that the standard methods of treatment of cardiac failure were used and that, despite that, there was inexorable progression. Then, we come to October, 1961, when there was a pleural effusion on the right side. This had me wondering why *right*, but I can see that there is also some effusion on the left side here (with reference to the x-ray film). I think we can say that this was an effusion of cardiac origin—the protein content is not over 3 Gm. per 100 ml.;

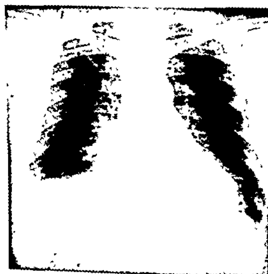


Fig. 3. X-ray film of the chest made on Jan. 23, 1962.

sounds were sharp and clear. No murmurs could be heard. The blood pressure was 140/90 mm. Hg. The liver was not enlarged. The pulses of the peripheral arteries were normal.

No other abnormality was found on general physical examination. His hair appeared to be normal, and there were no signs of thyrotoxicosis, past or present.

The electrocardiogram showed generally low voltage; the sum of the amplitudes of QRS in the standard limb leads was 10 mm. A ventricular extrasystole occurred after every two or three normal beats. The T waves were generally of low amplitude and were inverted in Leads V_4, V_5, and V_6. Another record made a few days later was unchanged, except that no extrasystoles were recorded.

X-ray examination of the chest showed general enlargement of the heart. Oblique views with opaque boluses showed no dilatation of the left atrium nor any other abnormal configuration. X-ray examination of the neck showed osteoarthritic changes with narrowing of the disk spaces between C_5 and C_6 and between C_6 and C_7. An osteophyte caused a little narrowing of the intervertebral foramen between C_5 and C_6 on the left side. X-ray examination of the elbows showed moderate osteoarthritic changes, more pronounced on the left side. The bones and joints of the hands appeared to be normal. Opaque-meal examination showed no abnormality of the esophagus, stomach, or duodenum.

The blood film appeared to be normal. The hemoglobin value was 16.4 Gm. per cent, and the leukocytes numbered 8,400 per cubic millimeter (neutrophils 47, eosinophils 2, lymphocytes 47, and monocytes 4 per cent). The erythrocyte sedimentation rate was slow (2 mm. in 1 hour—Hawksley). The lupus erythematosus phenomenon could not be elicited.

Biochemical tests of the blood gave the following values: serum sodium 138, potassium 3.6, calcium 5.2, inorganic phosphorus 2.3, chloride 98, bicarbonate 27 mEq./L.; uric acid 1.6 mg., urea 20 mg. per 100 ml.; cholesterol 140, bilirubin 0.6 mg. per 100 ml.; albumin 4.9, globulin 2.2 Gm. per 100 ml.; turbidity tests normal; serum alkaline phosphatase 8 King-Armstrong units. The test of liver function with Bromsulphalein showed a slight delay in the clearance of this substance. The Eagle flocculation test for syphilis was negative.

The urine contained no albumin, sugar, excess urobilinogen or 5-hydroxy indole acetic acid. It contained no cells nor casts nor microbes.

The intracutaneous tuberculin test yielded a reaction. The uptake of radioactive iodine indicated a euthyroid state. The Rose-Waaler test was positive in a titer of 1:1024. A test for C-reactive protein was negative. Liver biopsy produced normal liver tissue.

Treatment was begun with digoxin and chlorothiazide, and dietary salt was restricted, but this had no effect on the edema. An injection of mersalyl was found to produce a brisk diuresis, with subsidence of the edema; but the fluid would reaccumulate the next day.

A skin biopsy from one of the fingers showed hyperkeratosis and edema of the dermis. There was no sign of scleroderma. A muscle biopsy showed no abnormality apart from hyaline degeneration in the wall of one blood vessel. There was no sign of inflammation. A laryngeal biopsy also showed no sign of scleroderma or other morbid process. A liver biopsy was also made.

In view of the result of the Rose-Waaler test a provisional diagnosis of rheumatoid carditis was entered and the patient was discharged on Oct. 7, 1961, taking daily doses of digoxin, bendrofluazide, and potassium chloride, as well as prednisone (15 mg. daily).

Second admission. On Oct. 27, 1961, the patient was readmitted because of increasing breathlessness and crural edema. His liver was now distinctly enlarged. A pleural effusion on the right side was also present, from which just over a pint (600 ml.) of straw-colored fluid was aspirated, with great relief of breathlessness, which was not troublesome afterward—he could always lie flat without discomfort. The fluid contained 2.4 Gm. of protein, 570 mg. of chloride, and 140 mg. of sugar per 100 ml. Many of the investigations were repeated, with no significantly different results, except that the Rose-Waaler test was now reported to be negative. On December 13, biochemical tests of the blood gave the following results: sodium 126, potassium 3.6, chloride 86, bicarbonate 30 mEq./L. The blood urea level was 30 mg. per 100 ml. Pleural biopsy, performed when the fluid was aspirated, showed only "some swelling of the serosal cells."

Treatment was continued with digoxin, prednisone, and a variety of diuretic drugs. The signs of heart failure became gradually worse. On Jan. 9, 1962, a trial was made of spirolactone (100 mg. every 6 hours) for a week. There was a good diuresis for a day or two, but no notable improvement.

On Jan. 19, 1962, the right side of the heart was catheterized by way of a vein in the right arm. The following records were made of the pressure and oxygen content of the blood: *Pressures (in mm. Hg):* Right atrium—*a* wave 8, *x* wave 5, *v* wave 8, *y* wave −1, mean 6; pulmonary capillary mean 7; right ventricle—systolic 22, diastolic 8, mean 12; pulmonary artery—systolic 26, diastolic 12. *Oxygen saturation of hemoglobin:* Mid-pulmonary artery 47 per cent; mid-right ventricle 48 per cent, low right ventricle 47 per cent; mid-right atrium 49 per cent; high superior vena cava 48 per cent, low superior vena cava 52 per cent; femoral artery 95 per cent.

The tricuspid valve was in its normal position, and Ebstein's anomaly was excluded. X-ray films were made before the catheter was withdrawn, in an attempt to demonstrate any abnormal thickening of the wall of the heart, but none could be made out. No calcification of the pericardium could be detected.

On Jan. 22, 1962, the patient suffered a stroke, which deprived him of speech and paralyzed the right side of his body. A week later he died.

Discussion

DR. PUFLETT: Before I start, I would like to ask a question. I notice that the skin had become tight over the patient's fingers and had begun to crack. Was there any change of color there, Dr. Epps?

DR. EPPS: Yes, I think there was some

sarcoid. A bilateral central involvement of the ninth and tenth nuclei, sparing adjacent structures, would likewise be an unbelievable occurrence. I have suggested that we are dealing with an intrinsic weakness of muscle rather than neurogenic involvement, and I have suggested the possibilities. I want now to carry on further into this very difficult case.

The next thing I want to discuss is the observation that the patient looked younger than his years, that he was intelligent and alert, but that his face was curiously expressionless. Now, what makes a man look younger than his years? Sometimes it is absence of gray hair; but more to the point I think is the texture of the skin. The young man has a smooth face and we old fellows have wrinkles around our eyes, around our mouths, and on the sides of our necks. This man at 55 did not have that. Also, his face was expressionless. Now, if his face were smooth, abnormally for a man of 55, what would I think of—scleroderma, polymyositis? I wouldn't think of myxedema or any of the endocrine conditions, and if I thought of a man with a face that was immobile, I would think of facioscapulohumeral myopathy, dystrophia myotonica, or polymyositis with facial involvement. Again it would be most odd for sarcoid to do such a thing.

In my opinion, a fairly distinct diagnostic trend is now evolving in this case if I am putting the accent on the right things.

The next thing I want to discuss is the finding that the skin of his fingers was tight and cracked. The biopsy of this showed hyperkeratosis and edema of the dermis. There was no scleroderma. That, of course, does eliminate scleroderma. But it does not eliminate polymyositis or, as popularly considered, dermatomyositis. Pigmentation and edema are common pathologic findings of the skin in this collagen disease which involves many structures.

Another fascinating aspect of the case is the neurological symptoms. For some time he had numbness of his fingers and had noticed difficulty in doing up buttons. This numbness disappeared with diuretics. In my opinion, the symptoms do not resemble those of a lesion of a cervical disk. We read that all of his fingers were involved like a glove. With all due respect to the x-ray finding of a degenerative condition between C_5 and C_6 and between C_6 and C_7, it is my opinion that the numbness was due to some involvement of his digital nerves. It was not just an inflammatory condition; the nerves were also affected by edema because the symptoms could be reversed by diuresis. It was a peripheral neuritis due to some localized inflammatory lesion in the fingers.

Another interesting observation was the diagnosis of Bell's palsy, which cleared up in 3 days. I have not had very much experience with Bell's palsy, but I think that I have not seen it—a lower motor neurone lesion—resolve in 3 days. I do not think that it is possible for a lower motor neurone lesion to resolve in 3 days; so, I consider that there must have been something else happening. It could have been a small hemorrhage, somewhere around the facial nucleus on the left side.

And then, we have the terminal illness, right hemiplegia, and his death. What caused this—an embolus, hemorrhage, or thrombosis? I think that probably it was a hemorrhage. What else can I get from the investigations? The Rose-Waaler test was positive on one occasion and negative on the other. Rheumatic conditions, but also collagen diseases, can cause this; but of interest is the fact that it was positive on one occasion and normal on the other. Finally, there was the muscle biopsy which showed no abnormality apart from the hyaline degeneration in the wall of one blood vessel.

It is my opinion that this patient was suffering from a collagen disease, and that the condition was polymyositis involving the heart, the fingers, the pharynx, and the peripheral nerves in the fingers; but, as is usual, there was also an arterial fibrosis, which is frequently associated with small perivascular hemorrhages. I believe that his nervous condition was secondary to an associated vascular disease and caused his death from a cerebral hemorrhage. I think that this was primary myositis, not secondary to new growth; that is a not uncommon association, bronchogenic carcinoma being the most common, but I can see no sign in this case of any carcinoma being responsible. I regard it as primary myositis.

MODERATOR: Thank you, Dr. Puflett. Dr. Puflett has been willing to commit himself. Before I ask for any other suggestions as to

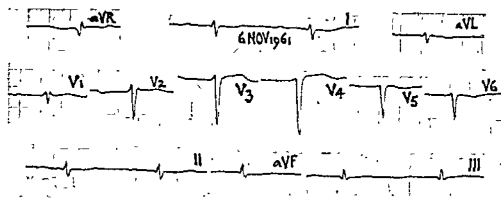


Fig. 4. Electrocardiogram recorded on Nov. 6, 1961. 1 cm. = 1 mv.

it is a transudate. Despite the most energetic treatment, this patient's cardiac failure progressed. The next thing is the further investigations, and it is hard to reconstruct the patient's condition from the information which emerged, since none of it is simultaneous. The catheterization was done well after some of the other clinical findings were made; but one can say that the findings were remarkably normal in regard to pressure, with just a slight increase over the normal or upper normal in the readings on the right side. The capillary (mean) pulmonary pressure was normal, which is interesting since there had been effusions and breathlessness; but, on the whole, the pressure readings give us very little, apart from indicating that there are some findings of right heart failure. The oxygen saturations are very much normal, with some lowering of the venous oxygen saturation, which also can be considered to be part of right ventricular failure. Now at this stage, I consider that we are dealing with a diffuse cardiac condition. I believe that this condition involves the right and left ventricles. As to the etiology of this diffuse condition, I would like to consider briefly a few suggestions or thoughts.

Is it coronary heart disease? A man of 51 is well within the age group. There is no chest pain, for whatever that fact may be worth; but, on the whole, I am not inclined to diagnose ischemia. I want to think in terms of a diffuse myocardial lesion, and the causes of a diffuse myocardial lesion. One can think of the various infections which include the Coxsackie myocarditis, brucellosis, histoplasmosis, and so on, and I think we can discard them. Then we can think of the collagen diseases, lupus erythematosus, polyarteritis nodosa, scleroderma, polymyositis, and, then, in addition, we can think of the endocardial fibroses, amyloid disease, hemochromatosis, and sarcoidosis.

Now, at this juncture let us look at some of the biochemical investigations. These are remarkably normal, and, although the values for the serum sodium and chloride are low in the second series, I do not regard them as significant in indicating the pathology. The points that I should like to make are that the potassium has been normal throughout, despite the congestive cardiac failure, and also the serum calcium, which might be pertinent in a case of sarcoidosis.

The next condition I wish to discuss is the huskiness of his voice and difficulty in swallowing which were noticed. The difficulty was in swallowing dry foods. It is most significant that our radiologist states that the radiopaque meal showed no abnormality of the esophagus, stomach, or duodenum. Since there was no abnormality of the esophagus, we can say that the difficulty in passing on solid foods lay somewhere else than in the esophagus, and I would suggest that it might have been in the pharynx. Now, what would cause difficulty in swallowing and in speaking in such a case? Well, first, a biopsy showed no scleroderma. That more or less eliminates a mucosal lesion. If we work from within outward, amyloid disease is still well in the running, polymyositis is still to be considered, and, also, any involvement of the peripheral nerves or even the cranial nuclei. A bilateral involvement of the peripheral nerves of the ninth and tenth cranial nuclei would be an unlikely coincidence, even for

a cerebral hemorrhage. Might it not have been an embolism after catheterization of the heart?

DR. EPPS: I believe that I must attempt to answer that. I have little doubt that the patient did have an embolism. It was extremely sudden. I thought that that was a strong point against constrictive pericarditis, but this sequence of events is not uncommon in some of the cardiomyopathies. And why did the patient perish? Well, he had gross and irreversible cardiac failure and a severe cerebral embolism which disturbed his state of consciousness for 24 hours, and he developed a superimposed chest infection.

DR. STUCKEY: Might I ask a question of Dr. Epps? Was there any history of chronic alcoholism?

DR. EPPS: We went into that question carefully. The patient assured us that he took very little alcohol. His wife confirmed that, and I saw no reason to doubt it.

DR. STUCKEY: The picture here, as Dr. Puflett has said, is one of diffuse myocardial disease with a progressive illness resulting in death. This is a difficult group diagnostically. A large number of possible etiological factors come in. It has been shown in recent years that quite a few of these patients have taken alcohol in substantial quantities over many years. In some people this causes irreversible myocardial changes which result in death. Apart from that group, there are many other etiological factors, a number of which Dr. Puflett has already mentioned—scleroderma, myositis, the various infiltrations, glycogen-storage disease, and so on. It is often difficult to reach a final diagnosis during life. Even at postmortem examination the result, at times, is still not clear. This is the group into which I think this patient would fall, and I believe that it is very difficult to reach a final diagnosis on the information available to us.

MODERATOR: Yes, quite.

DR. THOMAS: I am in the unfortunate position of knowing the diagnosis here, not through any subterfuge, but purely because I was called on to consider one facet of this case. Therefore, I will confine my remarks to that facet, and it does, I think, give a clue to the diagnosis. It is stated that the uptake of radioactive iodine indicated a euthyroid state. Now, some points in the history suggested that he was hypothyroid: the increased sensitiveness to cold, the dryness of the skin, the progressive dryness of the hair. Dr. Puflett mentioned the fact that his face was more youthful than his years, that is, not consistent with myxedema; but perhaps the lack of expression in his face was due to tautness of the skin with edema. That was presumably the cause of the numbness and swelling of his fingers, since it was reversed by diuretics. The use of the term "curiously expressionless" has the ring of a cliché about it, as though the person who wrote it was attempting to describe the patient in terms of a preconceived diagnosis. One gets the impression that, when this patient was admitted to the hospital, he was thought to have scleroderma, and that the use of some of these terms might have been due to prejudice.

Some features of the electrocardiogram were consistent with hypothyroidism. Now, it is not possible to exclude hypothyroidism by measuring the iodine uptake alone. It is not possible to state that a certain uptake of radioiodine indicates a euthyroid state. What can be said is that the rate of uptake of iodine as measured by this test is within the range usually associated with normal thyroid function. If the patient were in fact hypothyroid with a "normal" rate of uptake of iodine, then one might conclude that he had a goiter. We are not told whether one was felt in the neck. Is there any evidence in the x-ray films of thoracic goiter? I think that if we knew whether he had a goiter, that might assist in the diagnosis. I am not suggesting that the heart failure was due to hypothyroidism, but that the patient did show signs of hypothyroidism with a normal iodine uptake.

DR. AMOS: This patient's protein-bound iodine was also estimated (it does not appear in the protocol) and was found to be in the normal range.

DR. ISBISTER: I think that Dr. Puflett has given us a very good case for the diagnosis of diffuse cardiomyopathy. But I had the opportunity of seeing this patient, and I believe that not enough has been said about the possibility of his having had constrictive pericarditis. He had predominantly right-sided heart failure, which was not relieved by treatment, and, as Dr. Epps

diagnosis, I wonder whether Dr. Kalokerinos would like to comment on the x-ray films.

DR. KALOKERINOS: The abnormalities are not specific, except that the films do illustrate progressive heart failure. There is cardiac enlargement, but the heart is normal in configuration. In the early stages the lung fields are clear; later, we see effusions appearing, which are greater on the right. The lungs and vessels are normal. There is no evidence of cardiac or pericardial calcification, and in the other parts of the body that were x-rayed, elbows and the bones that we can see on the chest films, no significant radiologic abnormality is seen.

MODERATOR: Dr. Freeman, would you like to say something about the electrocardiograms?

DR. FREEMAN: On looking at this tracing, I get a different impression from that which was in the protocol. There is evidence here of right axis deviation, and there is almost complete absence of R-wave activity across the whole of the chest from V_1 to V_6. The voltage is certainly low. This is perhaps a nonspecific graph, in that the T waves are low and the voltage is low. In many aspects, however, it would be compatible with an old anterior infarction which, in the presence of congestive cardiac failure with effusion, has damped the voltage. I think that the protocol gives a misleading impression.

MODERATOR: Thank you, Dr. Freeman. I believe that Dr. Epps himself carried out the cardiac catheterization and at the time made some comments on differential diagnosis from the graphs and figures obtained.

DR. EPPS: Yes. First of all, the decision to carry out cardiac catheterization in this patient was deferred, as you will see from the dates. The reason for this was that I thought that there was some risk with such a degree of heart failure. Also, there was a possibility of some form of cardiac myopathy, and in the presence of those conditions cardiac catheterization is not well tolerated. But it was finally decided that we might obtain some evidence favoring or excluding constrictive pericarditis. This diagnosis was considered, of course, on the first admission. When the third chest film was taken on September 4, the heart was enlarged, although not markedly so; yet the patient had very gross right heart failure. Pericardial calcification was not seen; but it is seen in only about half the cases of constrictive pericarditis. The size of the heart increased considerably, which was a point against constriction, although we still did not think that it had been firmly excluded.

There were two maneuvers in the cardiac catheterization which we hoped would help us. One was the attempt to demonstrate the thickness of the pericardium by moving the catheter in the right auricle and ventricle and noting on the x-ray screen whether it could be brought into approximation with the outermost part of the cardiac border. In fact, this was the case, with the exception of a small area in the middle of the right atrium. This, we felt sure, excluded the possibility of any gross pericardial effusion and was a point against constrictive pericarditis, since there was no significant thickening of the pericardium.

Another point is that it is fairly characteristic of constrictive pericarditis that the pressures in the two atria are somewhat the same. We were able to establish that the pressures in the two atria were similar, and were raised moderately in both. This was at least consistent with constrictive pericarditis.

A third point to be analyzed was the role of pressure in the right atrium and the right ventricle. The characteristic negative pressure wave, known as the *y* trough, which is found in the pressure tracings on cardiac catheterization of the right atrium and right ventricle, was present, with the pressures stated in the protocol. This is not specific for constrictive pericarditis, since it is seen in other kinds of heart disease—gross right heart failure, particularly due to cardiomyopathy, and occasionally in gross mitral valvular disease. Any observation of this nature would not necessarily confirm a diagnosis of constrictive pericarditis, but, if absent, would be a strong point against it. To sum up, the catheterization findings were consistent with constrictive pericarditis with regard to the pressure curves and the left atrial pressure, but were rather against it in demonstrating the absence of any significant thickening of the pericardium.

MODERATOR: Why did this person die? Dr. Puflett has suggested that he suffered

differential diagnosis, but the other findings are difficult to correlate. Amyloid disease is associated with atrial involvement, more than any other. There was no atrial fibrillation in this case. Dysphagia is a common finding, and laryngeal involvement is also common; but with the biopsy reports available, I thought that this diagnois could not be entertained. I believe that the only diagnosis one can consider to cover this case is that of a collagen disease. I say polymyositis.

DR. PAYNE: The autopsy was performed 11 hours after death, and I can agree with the protocol that this man looked strikingly younger than his 55 years. There was no demonstrable subcutaneous edema, and external observation disclosed no other relevant feature. Now, I would like to confine myself mainly to the relevant positive findings at autopsy.

In the *brain*, there was a large area of softening in the left cerebral hemisphere in the parietal region. The vessels at the base of the brain looked healthy. The middle cerebral arteries were explored particularly, but we were not able to demonstrate any vascular lesion; however, this is often the case, since the vessels are end-arteries and the lesion is lost in the area of softening. The cerebral infarct was compatible with its occurrence a week before death. I will pass over the heart for a moment and go to the lungs. In the *lungs*, scattered bronchopneumonia was present, and quite a bit of fluid could be expressed from the lower lobes. The only fluid was 2 to 3 fluid ounces (50 to 100 ml.) in the cavities. Nothing else was observed in the lungs. The *liver* was quite congested and had a pattern consistent with cardiac cirrhosis. It weighed 4 pounds (1.8 kilograms); the normal weight is 3 pounds, 5 ounces (1.5 kilograms). As for the *kidneys*, the right kidney weighed 5 ounces (140 grams), and the notable feature here was a large infarct. I assume that there was no reference in the notes to indicate when this may have occurred, but it was a quite large infarct, involving about a third of the kidney; it was an old one and was quite well healed. The left kidney was larger and, no doubt, had hypertrophied to compensate for this.

In regard to the *pericardium*, there were no pericardial adhesions, and the cavity was quite free; there was perhaps 1 to 2 fluid ounces (30 to 60 ml.) of clear fluid in it. The heart was quite striking in that it was so large. It weighed 1 pound, 8 ounces (680 grams), whereas the normal heart weighs about 11 ounces (300 grams). The enlargement of the heart was seen to be general, with dilatation and thickening of the walls of all chambers. The right ventricular wall measured 7 mm. in thickness (Fig. 5). We measured this at the base at the narrowest part. The normal is 2 to 3 mm. The thickness of the left ventricular wall measured 13 mm., whereas the normal is 8 to 10 mm. The coronary vessels were patent. Moderate atherosclerosis was present, but the arteries had good lumina. A striking thing was the very fine translucent granularity on the endocardial and pericardial surfaces of the heart. This granularity was rather nodular on the valves. On the endocardial surface of the atria it was linear and very fine, and on the free margins of the mitral and tricuspid valves it was more nodular and rather like grains of sago (Fig. 5). On the pericardial surface this translucent granularity was most marked at the base of the heart (Fig. 6).

Apart from some symmetrical enlargement of the thyroid gland, no other abnormalities were found.

I think that now we should take a look at the sections. This first section is taken from the left atrium and shows the presence of a hyaline substance both in the endocardium and between muscle fibers. There is marked fibrous thickening of the endocardium. The hyaline substance stained metachromatically with methyl violet (Fig. 7) and is, therefore, amyloid. Other sections taken from the ventricular walls show conglomerate masses of amyloid replacing muscle fibers by pressure atrophy and ischemia. The surviving muscle fibers show hypertrophy. The deposition of amyloid was also present in the walls of small blood vessels and beneath the pericardium.

The sections of lung show bronchopneumonia, with deposits of amyloid in small blood vessels and in alveolar septa. The amyloid in the walls of the small arteries often almost completely obstructed the lumen. This may have some significance in regard to the marked thickening of the wall of the right ventricle.

pointed out, a number of the catheterization findings were in favor of this diagnosis. I think that the electrocardiogram is consistent with it also. Despite the fact that the x-ray films do not altogether fit in, and that there are certain other features that do not fit in at all, I would like to say that, having seen him clinically, I believe that this was a very distinct possibility in the diagnosis.

DR. KALOKERINOS: In constrictive pericarditis, one expects the x-ray films to show irregularity of cardiac borders with diminished or absent pulsation, limitation of movement and associated pleural thickening, and calcification in the pericardium. The heart is often not enlarged. Radiologically, this patient was not considered to be suffering from constrictive pericarditis.

DR. FREEMAN: The point was made that the patient had pigmentation of the skin. Thus, the question arises of hemochromatosis affecting the heart. It would be a very rare presentation, but I think that it ought to be added for completeness. Another point is that huskiness of the voice and dysphagia along with a nonspecific myocarditis make one think of primary amyloidosis. Again, this is not the full picture, but there have been reports of cases with only cardiac involvement.

MODERATOR: Why does the huskiness of the voice make you think of that?

DR. FREEMAN: Hoarseness due to infiltration of the larynx.

MODERATOR: Isn't hoarseness commonplace in patients with enlargement of the heart, particularly with enlargement of the left auricle?

DR. FREEMAN: He did not have left auricular enlargement.

MODERATOR: Did he not?

DR. ROWE: I should like to support Dr. Freeman's suggestion of primary amyloidosis. I am rather inclined against a diagnosis of collagen disease, because the erythrocyte sedimentation rate was normal and the serum globulins were also normal. The electrophoretic pattern of the plasma proteins has not been done. The suggestion of constrictive pericarditis, I know, was made. Some textbooks suggest that an alternative diagnosis of primary amyloid must be seriously considered in any patient who is thought to be suffering from constrictive pericarditis. He had a quiet heart, triple rhythm, nonspecific electrocardiographic changes, and the other change that Dr. Freeman has referred to as indicating the possibility of an infarct. Then again, the dysphagia and the hoarseness of the voice rather incline me to this diagnosis. A contentious point was the Rose-Waaler test. A titer of 1:1024 was very strongly positive, and a negative result later on is a little surprising. It is interesting to consider primary amyloidosis, since it is thought to be a disease related to plasma cells, one of the dysproteinemias. They say that most patients with multiple myeloma, if they survive long enough, will eventually develop amyloidosis. Now, it is interesting that in multiple myeloma, hyperglobulinemia is present, but when amyloidosis develops, the hyperglobulinemia tends to decrease. Examination of bone marrow was not made in this patient. But other cases have been described in which an increased plasma-cell population in the bone marrow has been found; this was associated with abnormalities of the serum proteins, and these patients developed primary amyloidosis. I am suggesting that even though the electrophoretic pattern of the plasma proteins was not determined, this patient, in the initial stages, did have abnormal globulins which were producing the positive reaction to the Rose-Waaler test, and they later disappeared during the course of the disease when he went into full-blown amyloidosis.

DR. EPPS: As to the question of hoarseness, the larynx of this man was examined by direct laryngoscopy. The finding was that he had a monilial infection of the larynx, which later extended to the pharynx. This was treated with antifungal drugs, with considerable improvement of the hoarseness but not complete recovery.

MODERATOR: Before I call on Dr. Payne to whisk away the seventh veil, would Dr. Puflett like to say a few more words?

DR. PUFLETT: I think that the discussion has been very relevant. Constrictive pericarditis was not mentioned in my differential diagnosis. Alcoholic cardiopathy, I should have mentioned. I did think of it, but I did not believe that a history of alcoholism would have been omitted from the protocol. Amyloid disease is certainly high up in the

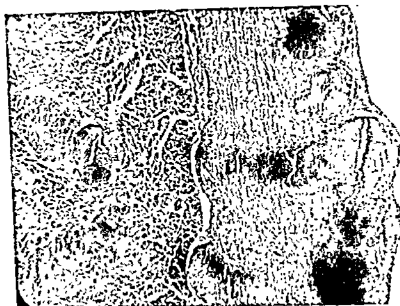


Fig. 7. Photomicrograph of a section through the left atrium, showing deposits of amyloid in the endocardium and myocardium Stained with methyl violet; magnification, ×60.

voltage, and often shows atrioventricular and intraventricular conduction defects; the T waves are generally inverted or flattened, and atrial fibrillation and ectopic beats are common.

It has been said that any refractory type of congestive cardiac failure in middle-aged men should lead the clinician to suspect cardiac amyloidosis. Once suspected, this diagnosis is still difficult to prove since no specific test for its confirmation exists. The Congo-red test is unreliable; a positive result does not give conclusive proof of amyloid, and a negative result does not prove its absence. Apart from these drawbacks, the test may be dangerous and lead also to unsightly red disfiguration of cutaneous deposits of amyloid.

As Dr. Rowe has mentioned, recent articles associate with amyloidosis an abnormal serum globulin which moves with the α_2 fraction. Suggestions have also been made that this may well represent the products of an immune mechanism.

Tissue biopsy remains the most reliable means at our disposal to make an early diagnosis of this disorder; but we have seen in this case that even five tissue biopsies did not disclose the nature of the patient's illness. It may well be that the wrong organs were submitted to biopsy. Most authors agree that lingual or gingival biopsies are the most rewarding. Macroglossia, in fact, is an important sign to look for in the examination of a patient with cardiomyopathy of obscure origin.

In closing, I would like to emphasize the fact that a disease is only as rare as the number of times the diagnosis comes to mind.

Clinical diagnosis: Constrictive pericarditis (?) Cardiomyopathy (?)

Dr. Puflett's diagnosis: Polymyositis affecting the heart.

Other suggested diagnoses: Alcoholic cardiopathy (Dr. Stuckey); hypothyroidism (Dr. Thomas); hemochromatosis affecting the heart (Dr. Freeman); primary amyloidosis (Dr. Freeman and Dr. Rowe).

Anatomic diagnosis: Primary amyloidosis; cerebral and renal infarction; bronchopneumonia.



Fig. 5. Photograph of the heart, showing "straiae" and "sago grains" of amyloid deposited beneath the endocardium of the right atrium and tricuspid valve. The wall of the right ventricle is greatly thickened.

There was a considerable amount of amyloid present in the section taken from the thyroid gland, both in the walls of the small blood vessels and in the fibrous tissue of the trabeculae of the gland. Other sections confirmed the microscopic findings, and amyloid was present in the walls of the blood vessels of all organs examined.

So, the postmortem diagnoses are: (1) primary amyloid disease, (2) cerebral and renal infarction, and (3) bronchopneumonia.

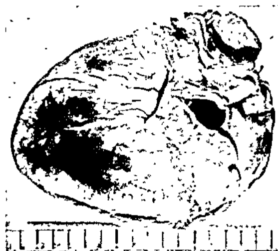


Fig. 6. Photograph of the heart, showing deposits of amyloid in the epicardium.

MODERATOR: Thank you, Dr. Payne. This has been a case of some rarity. Do you agree, Dr. Amos?

DR. AMOS: Well, up to about 1950, cardiac amyloidosis could well have been classed as rare; but since that time the number of cases reported in the literature has been so great that such a description is no longer justified. Primary amyloidosis, in contradistinction to secondary amyloidosis and the amyloidosis found in myeloma, occurs more often in the heart than in any other organ. Still, it is not often diagnosed during life. Our case today was no exception, and I think that all of us have gained considerably by the very clear discussion presented by Dr. Puflett.

Most authorities agree that primary cardiac amyloidosis causes refractory congestive cardiac failure, which often closely simulates constrictive pericarditis. The pathologic lesions produced are generally typical, in that there is gross involvement of the right atrium and often of the left, and, as in our case, of the ventricles as well. The lesions show as minute, raised, pinkish elevations which may coalesce to form plaques.

The electrocardiogram is usually of low

History

A long history of symptoms favors myocardial dilatation but does not exclude pericardial effusion. A history of diseases such as hypertension or syphilitic valvular disease or the postpartal state favors the former, whereas that of pulmonary tuberculosis or malignancy points to the latter.

Dyspnea, including orthopnea, is a complaint common to both states, but true paroxysmal nocturnal dyspnea is uncommon in uncomplicated pericardial effusion. Relief of dyspnea by sitting up and leaning forward and especially by assuming a position on the elbows and knees is highly suggestive of effusion. Dyspnea due to congestive failure is frequently relieved by sitting upright, but the benefits of leaning forward are not nearly so prominent.

Chest pain may be prominent in either myocardial or pericardial disease, but, again, relief by leaning forward is a striking feature of the latter. Pericardial pain is further suggested by its intensification with movement of the body, respiration, swallowing, or belching. At times, throbbing pain with each heartbeat may be observed, and at times the center of the pain may be located primarily on top of the left shoulder.[1]

Physical examination

On physical examination, the observation of the typical body position noted above and the presence of significant fever initially point to pericardial disease. Other physical findings may be of great help.[2,3]

Distention of the neck veins may be prominent in both states under consideration, but the finer characteristics of this distention can be of differential importance. On inspiration, the drop in intrathoracic pressure in effect "sucks" blood from the great veins, which is readily accepted by the right atrium, right ventricle, and expanded pulmonary vascular bed. This is manifested clinically in either the normal or dilated heart by a tendency toward collapse of the neck veins. In pericardial effusion with tamponade, a different finding is occasionally noted. Because the thoracic veins are largely extrapericardial, blood is sucked into them during inspiration, but in the case of pericardial tamponade, emptying or filling into the right side of the heart is inhibited. This causes the paradoxical "inspiratory distention of the neck veins," or "Kussmaul's sign." Another hemodynamic factor in the production of this condition may be the peripheral venoconstrictive reflex associated with inspiration.[4] When present, this sign is beneficial in the diagnosis of pericardial tamponade, but it may also be seen in other causes of central venous obstruction, e.g., in the "superior vena cava syndrome" or constrictive pericarditis. It should be emphasized that it is frequently impossible to detect this sign clinically, particularly in patients in whom there is marked venous distention with the neck veins fully filled to the angle of the mandible.



Fig. 1. Teleoroentgenogram of a 28-year-old Negro woman who complained of dyspnea.

The recording of *arterial blood pressure* may be helpful. In both primary myocardial disease and pericardial cardiac tamponade there is a tendency for the systolic pressure to fall, for the diastolic pressure to rise slightly, and, especially, for the pulse pressure to narrow. A *narrowed pulse* pressure is then of little value in differential diagnosis, although it is extremely useful in gauging the severity of the underlying hemodynamic alterations.

Methods in the diagnostic differentiation of myocardial dilatation from pericardial effusion

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The problem of differentiation of pericardial effusion from generalized cardiac dilatation is common and often difficult. A typical case in point is that of the patient with symptoms and signs of congestive heart failure in whom the teleoroentgenogram of the chest shows moderate to marked enlargement of the cardiac shadow (Fig. 1). Underlying this enlarged shadow might be pericardial effusion or myocardial dilatation or a combination of both processes (Figs. 1 and 2). The patient may complain of severe dyspnea and have edema and marked distention of the neck veins. The diagnosis of pericardial or myocardial disease is of obvious and immediate importance, both from the standpoint of treatment and prognosis. The presence of pericardial effusion might be readily established by pericardial paracentesis, but one hesitates to employ this procedure when the possibility of myocarditis or myocardial degeneration exists. In such patients, the flabby, friable myocardium is particularly vulnerable to the probing needle. In the acute treatment of severe dyspnea of myocardial failure, one hesitates to employ phlebotomy if pericardial effusion with cardiac tamponade is not excluded. In the latter, a decreased venous cardiac filling pressure may be lethal; in fact, in the past, intravenous fluids were used occasionally to augment filling pressure in the treatment of such patients. Digitalis may be helpful in the treatment of myocardial failure, but would be of no value and might even be harmful in the presence of cardiac tamponade because of decreased venous filling pressure.

This problem of differential diagnosis is a real one. The following discussion attempts to outline procedures whereby this differentiation might be safely and accurately achieved. Pertinent aspects of the history, physical examination, and laboratory procedures are presented. For orientation, the various causes of myocardial dilatation and of pericardial disease are noted (Tables I-III). Apparently, the group of more uncommon causes of myocardial disease most frequently present the problem of excluding pericardial effusion. Some of the etiological factors may be responsible for either myocardial or pericardial disease, or both. It is interesting that, of the more common causes of pericarditis, rheumatic fever and uremia rarely cause effusion which progresses to cardiac tamponade severe enough to necessitate pericardial paracentesis.

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blood is accommodated, and, thus, there tends to be relatively less volume flow to the left side of the heart. During expiration, reverse events tend to take place on both the right and left sides of the heart. One might consider the analogy of the lungs as a "sponge" so that the filling of the left side (and left ventricular output) is decreased on inspiration and increased on expiration. The abnormal pulsus paradoxus is viewed simply as an exaggeration of this phenomenon. In pericardial tamponade, the increased venous return during inspiration cannot be translated into increased right ventricular cardiac output because of the obstruction to inflow. On the other hand, the augmented pulmonary vascular capacity during inspiration causes a decreased filling of the left side of the heart, which in this case is not compensated for somewhat by the normally present increased right ventricular output.

Recently, observations have been made on human pericardial tamponade under experimental conditions.[5] Interpretations from these studies explained the paradoxical pulse on the basis of "effective filling pressures." Of importance is the effective filling pressure of the left ventricle, which is governed by the pressure gradient from the pulmonary veins to the left ventricle. A distended, tight, fluid-filled pericardial sac reduces to a large extent the effectiveness of transmission to the left ventricle of the increased negative intrathoracic pressure during inspiration. This increased negative pressure, however, is transmitted to the pulmonary veins and capillaries, and, thus, the pressure gradient between the pulmonary veins and the left ventricle is decreased (a decreased effective left ventricular filling pressure). This results in decreased left ventricular output on inspiration.

Other recent studies have been made and interpreted as showing that inspiratory traction on the pericardium is the major factor in the production of both pulsus paradoxus and inspiratory distention of neck veins.[6] On six cadavers it was shown that when the pressure in the pericardial sac was raised by infusion of water, traction on the diaphragm (artificial descent) caused this pressure to rise significantly higher. Since the pericardium is joined

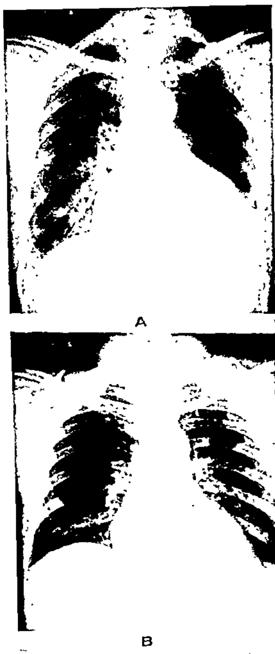


Fig. 3. Chest x-ray films of two patients taken shortly before death and subsequent autopsy, showing nonspecific enlargement of the cardiac shadow. Both patients had hypertension, uremia, and left ventricular hypertrophy; *A* had no significant pericardial effusion, whereas *B* had 250 c.c. of pericardial effusion. From the films, one might suspect the chance for pericardial effusion to be greater in *A* than in *B*. At autopsy, however, Patient *B* was found to have an effusion, whereas Patient *A* did not.

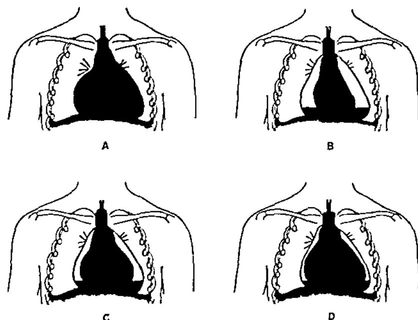


Fig. 2. Diagrammatic representation of the possible value of pericardial paracentesis and diagnostic pneumopericardium in the clinical study of heart size in the presence of varying amounts of pericardial fluid. *A*, Routine teleoroentgenogram showing a large cardiac silhouette. *B*, Enlargement is shown to be due to pericardial effusion with normal underlying heart. *C*, Enlargement of the cardiac silhouette due to both pericardial effusion and cardiac enlargement. *D*, Enlargement of the cardiac silhouette due predominantly to cardiac enlargement, with only small amounts of pericardial fluid.

A phasic decrease in the blood pressure on inspiration and a subsequent rise on expiration, the so-called "*pulsus paradoxus*," is an extremely important finding. The magnitude of the respiratory pressure excursions may be determined by the routine cuff recording of blood pressure in the arm, and normally it should not exceed 8 mm. Hg during *normal* respiration. With practice, one may detect variations of this order by ordinary palpation of the radial artery. Pulsus paradoxus is important because it is virtually a constant finding in pericardial tamponade. Certainly, if one fails to detect this during *exaggerated* inspiration and expiration, then tamponade is effectively excluded. It should be noted that, although the paradoxical pulse may be a constant finding in tamponade due to effusion, it is not specific for this. It may be found in constrictive pericarditis and also in other diseases, e.g., severe congestive heart failure and in any condition which increases the inspiratory negative pressure in the thorax or decreases pulmonary compliance, such as tracheal obstruction, pulmonary fibrosis, pleural effusion, etc. With pulsus paradoxus, systolic pressure, diastolic pressure, and pulse pressure decrease during inspiration.

The mechanism of the paradoxical pulse is not clearly understood. It is described as not being paradoxical at all, but rather just an exaggeration of normal hemodynamic events coincident with respiration. The normal person tends to have a "paradoxical pulse" because the increased venous return to the heart during inspiration is outweighed by the greater volume of blood accommodated in the chest, which, in turn, results in a decreased left ventricular filling and output. During inspiration, the diaphragm descends and the intra-abdominal pressure increases, whereas the expanding thorax and descending diaphragm reduce intrathoracic pressure. This has the effect of "pushing" and "sucking" blood into the right side of the heart. With respect to the left side of the heart during inspiration, the vascular capacity of the pulmonary bed is increased, more

more significant it becomes. A dilated left ventricle causes no dullness in this area, and a dilated right ventricle causes dullness only at the lowest portion of the sternum, rarely extending above the level of the fifth costal cartilage. Dilatation of the right atrium causes dullness in a small area adjacent to the sternum in the right fifth intercostal space.

Auscultation of the heart may be rewarding. Distant heart sounds are found with effusion, whereas prominent sounds favor myocardial dilatation. As with the apical impulse, there are frequent exceptions to this rule. The sounds may be quite loud in some patients with tamponade.

The detection of a pericardial friction rub is of obvious value. The rub may disappear when effusion occurs or, in some instances, it may remain even in the presence of a large effusion. Pericardial rubs are occasionally misdiagnosed as "to-and-fro murmurs."[4] This error may be avoided by recognizing the characteristics of rubs which have a scratchy, shuffling quality, with frequency components higher than most heart murmurs. The friction rub sounds superficial and closer to the ear and is accentuated by firm pressure from the stethoscope chest piece. Furthermore, friction rubs frequently have three distinct components, the first related to atrial systole (presystolic), the second to ventricular systole, and the third to early mid-ventricular diastole. With auricular fibrillation, only two components can be heard (ventricular systole and diastole) or, occasionally, only one component (ventricular systole). It is suggested that with a normal sinus rhythm, the persistence of a systolic component alone generally eliminates the possibility of a pericardial rub as the cause of a scratchy sound.[1]

The detection of a gallop rhythm implies congestive failure and is of obvious value. Details of gallop rhythm are presented elsewhere.[5] Suffice it to say that these gallops may be either protodiastolic (third heart sound or ventricular gallop) or presystolic (fourth heart sound or atrial gallop). Gallops may emanate either from the left or the right side of the heart. By various observations, these details may be detected at the bedside. Of greatest value is the detection of a left ventricular protodiastolic gallop, since it strongly favors left ventricular failure.

A rather common occurrence in left ventricular dilatation is the presence of an apical, low-pitched, diastolic "roaring" murmur. It is a "roar" rather than a "rumble," and this characteristic is of much help in its identification. It is frequently missed and must be carefully sought by utilizing the "bell" of the stetho-

Table I. Causes of myocardial dilatation

A. *Common causes*
1. Hypertension
2. Arteriosclerosis
3. Syphilis
4. Rheumatic fever
5. Thyrotoxicosis and myxedema
6. Congenital defects
7. Cor pulmonale
8. Anemia

B. *Uncommon or "exotic" causes*
1. Myocarditis
   a. Bacterial
   b. Rickettsial
   c. Viral
   d. Physical and metabolic
   e. Idiopathic
2. Post partum
3. Collagen diseases
4. Endocardial fibroelastosis
5. Endomyocardial fibrosis
6. Idiopathic hypertrophy
7. Familial cardiomegaly
8. Löffler's endocarditis
9. Hypersensitivity and autoimmunity
10. Alcoholic myocardiopathy
11. Nutrition
12. Sarcoidosis
13. Glycogen storage
14. Muscular dystrophy
15. Friedreich's ataxia
16. Gargoylism
17. Amyloidosis
18. Hemochromatosis
19. Beriberi
20. Presbycardia
21. Paget's disease
22. Neoplasia (primary and secondary)
23. Unknown

with the diaphragm, then on inspiration the pericardial sac is made longer, thinner, and more tense. This serves as the cause for the rise in venous pressure and impaired cardiac filling on inspiration in cases of pericardial effusion with tamponade. This explanation certainly appears to be a major factor in the production of the findings.

When searching for a paradoxical pulse, one should remember the effect of sinus arrhythmia on cardiac stroke output. The tachycardia during inspiration may tend to decrease the stroke output and systolic pressure, whereas the bradycardia on expiration may increase stroke output and systolic pressure.

As noted above, the decreased pulmonary compliance, such as is encountered in pulmonary emphysema and fibrosis, may produce an exaggerated paradoxical pulse. The neck veins provide a helpful distinction between pulmonary and pericardial disease in this type of patient. Because of the augmented negative intrathoracic pressure during inspiration in pulmonary disease there is usually an [illegible]aggerated collapse of the neck veins [illegible]uring this phase. This is in marked contrast to inspiratory distention noted in tamponade.

Another helpful diagnostic sign obtained by recording blood pressure is *pulsus alternans*. This is the alternation of a weak beat with a strong beat in the presence of a regular rhythm. The magnitude of difference between the weak and the strong beats is determined by careful measurements of blood pressure. Any detectable pulsus alternans is abnormal. Although it usually means left ventricular failure, it also may be present in cardiac tamponade. The important point here, however, is that in the case of tamponade an accompanying pulsus alternans tends to be minimal, whereas the paradoxical pulse is quite prominent. In left ventricular failure, if both types of pulses are present, the reverse is true. When both types of pulses are present in the same patient, one usually has to have the patient suspend respiration in the resting position in order to clarify the pulsus alternans. In the presence of auricular fibrillation or other irregular cardiac mechanisms, accurate determination of either a pulsus paradoxus or pulsus alternans is exceedingly difficult. In pulsus alternans, other accompanying findings occasionally noted are alternation in the intensity of the first sound, alternation in friction rubs and murmurs on auscultation, and electrical alternans in the electrocardiogram (see below).

Examination of the chest and lungs may offer rewarding findings in the differential problem under consideration. If a large heart shadow is observed on the x-ray film, the presence of clear lungs on auscultation is somewhat in favor of pericardial effusion. The detection of an area of dullness, bronchial breathing, and bronchophony at the base of the left lung (Ewart's sign) is a strong clue for the diagnosis of pericardial effusion. It is rarely present in congestive heart failure.[2]

Inspection of the anterior chest wall may be helpful in diagnosis. A prominent cardiac apical impulse favors a diagnosis of myocardial dilatation, whereas a diminished or absent impulse suggests a diagnosis of pericardial effusion. There are certainly exceptions to this, however, since tamponade may exist with a very prominent apical impulse. Occasionally, on palpating the chest wall in a case of effusion, one gains the impression of applying his hand to a fluid-filled balloon which is being set in motion by mechanical impulses—a sensation of "after-impulses." When an apical impulse is present, observations relative to the area of percussible cardiac dullness may be helpful. When the apical impulse is significantly medial to the outer border of dullness, effusion is suggested. Furthermore, percussible increase in the width of cardiac dullness at the base of the heart when the patient is supine is an occasional but not too reliable sign of effusion. It has been emphasized recently that percussion of the sternum and precordium yields information characteristic enough to suggest strongly the diagnosis of pericardial effusion (versus myocardial dilatation) in over 50 per cent of the cases in which it is present.[7] These findings are concerned with an area of marked dullness or flatness over the lower half or more of the sternum, an area which normal[illegible] a resonant note to percussion. [illegible] the dullness extends, the

(see above). Contrariwise, a drop in venous pressure during inspiration favors myocardial dilatation, especially if the pressure is very much elevated.

The *routine chest x-ray film* may be of help, but frequently one just observes a nonspecific enlargement of the cardiac shadow, which could be due to either myocardial or pericardial disease, or both (Figs. 1,2, and 3). The difficulties and poor successes in the roentgenographic differentiation between the dilated heart and pericardial effusion have been stressed repeatedly.[10,11] The typical "water-bottle" heart may occur in either process, as may the change in cardiac contour and widening of the base with movement from the erect to the supine body position. Of more value in the case of effusion is the absence of the usual contours of the cardiac border, viz., the pulmonary conus, the left atrial appendage, and the junction of the superior vena cava and right atrium. With enlargement of the cardiac shadow, the presence of clear lung fields favors effusion, but this may also be observed in primary myocardial disease, especially if tricuspid insufficiency is present. Whether or not the right cardiophrenic angle is acute or obtuse has not been too helpful.

On *fluoroscopy*, diminished pulsations may be detected in either effusion or myocardial dilatation. The detection of good pulsation in association with a large heart shadow, however, favors myocardial dilatation, as does the detection of a distinct P.O.P. (point of opposite pulsation) along the left cardiac border. The presence of a wavy undulation along the left border slightly favors effusion, but it also may be observed not infrequently in myocardial dilatation or in large lateral myocardial infarctions. The paradoxical movement of a ventricular aneurysm would not be expected in uncomplicated pericardial disease. During the Valsalva maneuver the normal heart shows progressive diminution in size. This trend is absent in the case of large effusions and usually also in myocardial dilatation. Occasionally, however, in the latter condition a significant decrease in size may be observed. This would not be expected in the case of tamponade.

When normal sinus rhythm is present, observations of the right atrial pulse may be helpful.[12] Normally, this consists of "two in and one out" or a "pause" on the instroke. These movements correlate with atrial systole, ventricular systole, and then ventricular diastole. Observation of this is favored by prolonged atrioventricular conduction time (prolonged P-R interval on the electrocardiogram). In pericardial effusion this typical right atrial pulse is lost, whereas in myocardial dilatation it is frequently preserved.

The *electrocardiogram* may be of great help in differential diagnosis. Changes typical of pericarditis (Figs. 4 and 5) are of obvious value, but frequently only "nonspecific T-wave changes" are present. Remember that the S-T and T-wave changes of pericarditis are in reality due to "epimyocarditis," and, thus, these changes persist when effusion develops, although the pericardial friction rub may disappear.

Decreased QRS voltage is a frequent finding in pericardial effusion, but it may also be present in primary myocardial disease, particularly if edema, pleural effusion, or marked pulmonary emphysema is present or if there has been loss of ventricular muscle. The presence on the electrocardiogram of evidence of bundle branch block, specific chamber enlargement, myocardial infarction, arrhythmias, and sinus tachycardia out of proportion to fever or lowered blood pressure, favors myocardial dilatation but obviously does not exclude pericardial effusion.

Of great value on the electrocardiogram is the detection of an electrical alternans.[2,13]

Table III. Estimated incidence of common types of pericarditis

Type of pericarditis	*Per cent*
Rheumatic fever	15-50
Bacterial (suppurative)	15-20
Acute nonspecific idiopathic	10-25
Uremic	15-20
Associated with myocardial infarction	10-15
Tuberculous	7
Neoplastic	7
Collagen disease	3
Traumatic	3
Other	1

*Table II. Causes of pericarditis**

A. *Idiopathic pericarditis*	
B. *Infectious pericarditis*	
1. Bacteria	4. Infectious mononucleosis
a. Suppurative	5. Fungus
b. Tuberculous	6. Parasites
2. Virus	7. Syphilis
3. Atypical pneumonia	
C. *Pericarditis in vasculitis—Connective tissue diseases*	
1. Rheumatic fever	6. Dermatomyositis
2. Lupus erythematosus	7. Steroid withdrawal reaction
3. Rheumatoid arthritis	8. Polyarteritis
4. Ankylosing spondylitis	9. Thrombotic thrombocytopenic purpura
5. Systemic scleroderma	
D. *Pericarditis in hypersensitivity states*	
1. Serum sickness	3. Other sensitivity reactions
2. Allergic granulomatosis	
E. *Pericarditis in disease of contiguous structures*	
1 Myocardial infarction	2. Dissecting aneurysm
a. Acute myocardial infarction	3. Pulmonary embolism
b. Postmyocardial infarction syndrome	4. Esophageal disease
c. Ventricular aneurysm	
F. *Pericarditis in disorders of metabolism*	
1. Renal failure	4. Addison's crises
2. Myxedema	5. Diabetic keto-acidosis
3. Cholesterol pericarditis	
G. *Pericarditis in neoplasia*	
1. Primary	
2 Secondary (direct or metastatic)	
H. *Traumatic pericarditis*	
1. Direct (penetrating)	
2 Indirect (nonpenetrating; irradiation)	
I. *Pericarditis of uncertain origin*	
1. Postpericardiotomy syndrome	6. Sarcoidosis
2. "Postoperative pericarditis"	7. Silicosis
3 Reiter's syndrome	8. Myeloid metaplasia
4. Whipple's disease	9. Sjögren's syndrome
5. Löffler's syndrome	

*Modified from Spodick.[3]

scope applied with very light pressure to the chest wall.[8]

In either congestive failure or pericardial tamponade, one may occasionally detect an alternation in the intensity of the mitral first heart sound. When this exists without pulsus alternans, then tamponade is favored. When it is present in congestive failure, pulsus alternans is usually present.

When specific valve murmurs are prominent, for example, in aortic insufficiency or mitral stenosis, then myocardial dilatation becomes the favored diagnosis.

Routine laboratory procedures

Determinations of *venous pressure* reveal increased pressure in cardiac tamponade and usually also in myocardial dilatation, so that it is usually not of great differential value. At times, however, one may detect inspiratory increase in venous pressure, which then favors pericardial tamponade

tions in intravascular pressure and pulse contours may also be noted.[15] Cardiac catheterization, however, is not without danger, and it has not been found to be necessary in the differential diagnosis under consideration.

Positive contrast angiocardiography has been employed with success in this problem by demonstrating a discrepancy between the size of the opacified cardiac chambers and the over-all cardiac shadow.[16] Again, this procedure is not without hazard, and it has not been found to be necessary in the present problem.

Recently, an *isotopic method* for the differentiation of massive pericardial effusion from cardiac dilatation has been employed with success.[17] By means of I^{131} albumin and precordial counting, calculation of the intracardiac blood volume is made. This is compared with the size of the over-all cardiac shadow determined radiologically, and a significant discrepancy implies effusion. This is an innocuous and simple procedure if adequate equipment is available. Scintillograms of the heart may also be used to determine the presence of pericardial effusion,[18] but the apparatus required is still more complex and expensive.

At present, of the more specialized procedures, *intracardiac negative-contrast carbon-dioxide roentgenography* (angiocardiocarbography) appears to be preferred. It is safe, quick, simple, and reliable and requires only equipment which is readily available in any hospital. Details of this procedure and methods of interpretation have been outlined previously.[19,20] Briefly, it consists of the intravenous injection of carbon dioxide in a patient placed in the left lateral decubitus position (right side up). A six-foot chest film is taken a few seconds after the injection, and the events are demonstrated radiographically. The carbon-dioxide gas in the heart rises to outline the uppermost border of the right atrial cavity. One then determines the thickness of the "right atrial band" (that area between the radiolucent lung above and the carbon-dioxide bubble below, composed of pleura, pericardial sac with any contained fluid, and right atrial wall). Accumulation of pericardial fluid causes a widening of this band (Fig. 7), as opposed to myocardial dilatation, in which the band retains its normal thickness of less than 5 mm. Because of specific gravity relationships, when pericardial fluid is present, the heart tends to assume a dependent position, so that, in general, the thickness of the band relates quantitatively to the amount of fluid present. Because of this, associated myocardial dilatation may be suspected in certain cases, even in the presence of the pericardial fluid (Fig. 8).

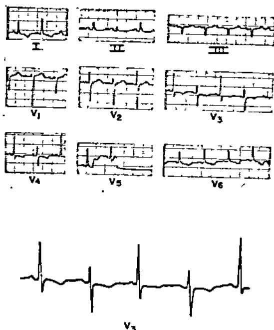


Fig. 6. Electrocardiogram demonstrating complete electrical alternans in which both the P and QRS complexes participate, in a patient with pericardial effusion and tamponade due to metastatic bronchogenic carcinoma. P-wave alternation is seen best in Lead V_3.

Pericardial paracentesis

The indications for pericardial paracentesis are (1) the confirmation of the diagnosis of pericardial effusion, (2) the immediate treatment of cardiac tamponade, (3) the local treatment of any underlying disease, such as the instillation of cytotoxic drugs for malignant involvement of the pericardium, and (4) isolation and identification of offending organisms, neoplastic cells, and characterization of the fluid for clinical diagnosis and management.

For diagnosis, fluid may be obtained for

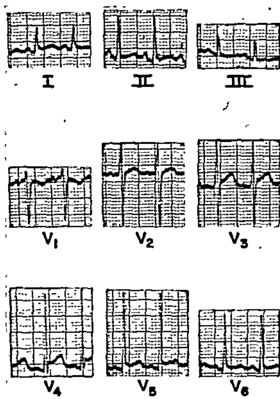


Fig. 4. Electrocardiogram taken during the acute phase of pericarditis due to Boeck's sarcoid, proved at autopsy.

This may be of the incomplete variety, wherein only the QRS complexes participate, or of the complete variety, in which both P waves and QRS complexes participate. T waves may also alternate. Incomplete electrical alternans may be seen either in pericardial tamponade or in primary congestive heart failure, but its presence in the latter is frequently accompanied by a pulsus alternans. Certainly, electrical alternans which occurs without a paradoxical pulse is a strong point in favor of myocardial failure. The complete variety of electrical alternans is of more specific value since it is virtually diagnostic of pericardial effusion (Fig. 6).[3] Alternation in the P wave may be very minute and easily overlooked, but its detection is of much importance. At times it may be necessary to have the patient suspend respiration temporarily while the electrocardiogram is taken, in order to eliminate respiratory-induced changes in cardiac position as a cause of apparent alternation. It is interesting that complete electrical alternans is usually seen only in cases of tuberculous or malignant effusion, and then only when effusion is severe with tamponade.

Why electrical alternans occurs in pericardial effusion is unclear, but it is postulated that a rotatory pendular motion of the heart with specific temporal relationships is set up by the swinging of the heart in the fluid-filled pericardial sac. This then produces alternations in the spatial orientation of the cardiac vectors as the heart beats mechanically. It is interesting that in pericardial tamponade, removal of as little as 10 to 20 c.c. of fluid by pericardial paracentesis may abolish the electrical alternans. Likewise, the pulsus alternans and alternating mitral first sound which occasionally accompany pericardial tamponade may disappear and the paradoxical pulse become significantly less after only small amounts of fluid are removed.

Special procedures

Cardiac catheterization may be used in the diagnosis of pericardial effusion by noting the anatomic relationship between the cardiac catheter applied to the right intracavitary border of the heart and the right border of the over-all cardiac shadow as demonstrated radiologically.[14] Altera-

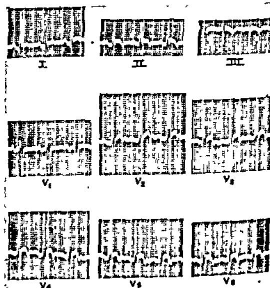


Fig. 5. Electrocardiogram taken during the acute phase of a traumatically induced hemorrhagic pericarditis established at operation.

inserted in the angle between the xyphoid process and the left costal margin and is directed inward and upward toward the left shoulder, keeping it close to the chest wall. This affords an extrapleural approach and provides maximum dependency for drainage. The disadvantage of this approach is that the needle must traverse relatively dense tissue which has a tendency to "give" suddenly while the needle is being directed toward the relatively thin and easily lacerated right ventricle and right atrium. Furthermore, the coronary vessels in this area are larger than those over the apex of the heart.

Except as noted above, the apical approach is our usual choice. Here one is less likely to tear a large coronary vessel, and, furthermore, the needle is being directed toward the relatively thicker left ventricle. One usually chooses a site approximately 2 cm. lateral to the apex beat or just medial to the left lateral border of cardiac dullness in the fifth intercostal space. The needle is inserted just over the upper costal margin and is directed inward and medially and slightly upward toward the spine.

The over-all procedure for paracentesis is usually as follows: The patient is premedicated with morphine or another suitable drug and is placed in the sitting position with his back supported. Incidentally, angiocardiographic studies have shown that when the patient is in the sitting position, the pericardial fluid tends to be located anteriorly and the heart posteriorly,[21] an ideal situation for pericardial tap. The tap site is selected and the skin area prepared as usual. A skin wheal is made with procaine and then the underlying tissue is infiltrated by means of a long No. 20 gauge needle with a short bevel. During this procedure, one frequently establishes the diagnosis of effusion using this small-caliber needle, but it is impractical to remove large amounts of fluid with a needle of this size. The pericardial depth is usually found at about 2 cm. from the skin surface in these cases.

Electrocardiographic monitoring probably should be a routine procedure during pericardial tap.[22] Here the extremity electrodes are placed in the usual manner, and the precordial or exploring electrode wire of the "V" lead is connected to the exploring pericardial needle. This attachment may be devised from a hemostat and adhesive tape or from a short wire with alligator clamps on each end, or a special pericardiocentesis electrode may be obtained.[23] Occasionally, one encounters some difficulty in obtaining a stable base line, but this is not usually a major problem. By electrocardiographic monitoring of this type, in addition to the early detection of

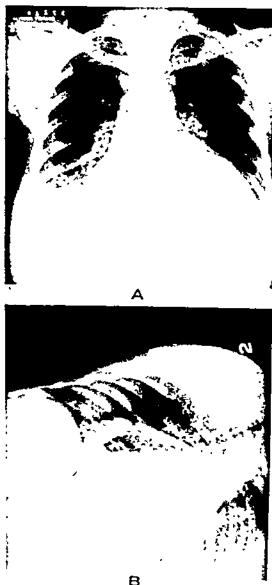


Fig. 8. Combined pericardial effusion and myocardial dilatation in a patient with postpartal myocardial degeneration. *A*, Erect film. *B*, Lateral decubitus film, after injection of carbon dioxide.

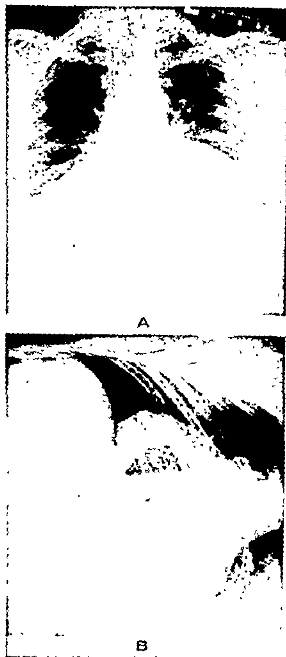


Fig. 7. Massive pericardial effusion due to myxedema, demonstrated by intracardiac carbon-dioxide roentgenography (angiocardiocarbography). *A*, Erect posterior-anterior film *B*, Left lateral decubitus film, after intravenous injection of 100 c.c. of carbon-dioxide gas. Marked thickening of the "right atrial band" is evident. Consult text for details.

detailed studies. Furthermore, air may be injected into the pericardial sac and subsequent roentgenographic studies made in order to confirm the localization of fluid to this area, to estimate the underlying heart size, and to observe the characteristics of the pericardium itself (Fig. 2).

In the decision of when to do pericardial paracentesis for relief of tamponade, several criteria are useful: (1) *Pulse pressure:* This has been one of the most useful criteria, and, in general, pericardial tap is indicated when the pulse pressure falls to 20 mm. Hg or less. (2) *Venous pressure:* In cases in which a tap is indicated, the venous pressure will usually exceed 150 mm. of water. (3) *Severe pulsus paradoxus:* The magnitude of the paradoxical pulse correlates grossly with the severity of the hemodynamic alteration. In severe cases the pulse may completely disappear on inspiration. (4) *Electrical alternans on the electrocardiogram:* In general, this correlates with a severe degree of pericardial effusion with tamponade. (5) *General signs and symptoms:* These may well influence the decision to undertake pericardial tap—for example, in the patient who demonstrates cold, clammy extremities, with a rapid pulse, mental disorientation, dyspnea, cyanosis, and decreased output of urine. The latter is a sensitive indicator of adverse hemodynamic alterations, and in severe cases the flow of urine, obtained from a catheter in the bladder, will be less than 0.5 c.c. per minute.

It is interesting that the above-mentioned findings indicative of pericardial tamponade may be reversed by the removal of very small amounts of fluid (10 to 20 c.c.) from the pericardial sac. Pressure-volume relationships are such that this might well be expected. Normally, the pericardial sac contains about 20 to 50 c.c. of fluid, and it probably has a capacity of about 80 to 100 c.c. without detectable cardiac compression, even under close observation. As little as 150 to 250 c.c. of fluid acutely collected, however, may cause significant cardiac tamponade, whereas in chronic cases, as much as 3,000 c.c. may be present without significant symptoms.

In general, we have employed two special sites for tap with success, but other sites have been suggested.[3] The xyphoid approach is usually indicated in cases in which purulent pericarditis is suspected or in cases in which left pleural or pulmonary disease exists. The needle is usually

usually employs a short-beveled No. 18 or No. 16 gauge needle, or an even larger one (depending on the type of fluid present), attached to the electrocardiograph as noted and connected through a three-way stopcock (for repeated emptying of the syringe) to a large syringe. A hemostat clamped to the needle at the skin surface may be used for the electrocardiographic connection and may also be used to limit the advance of the needle. The needle is advanced slowly in increments while one pauses in-between to watch for electrocardiographic changes. These changes may be delayed a few seconds, so that it is wise to pause a short while before each advance. When the needle touches the left ventricle, one may note a palpable impulse transmitted to the syringe or may feel a typical "chinking" sensation as the point of the needle scratches the ventricular surface.

When fluid is obtained, it should be removed slowly, in order to avoid acute myocardial dilatation and also the so-called "pleural" or "pericardial" shock syndrome.

As noted above, one may decide to instill air into the pericardium. A safe volume is anything less than the volume of fluid being removed. To avoid rapid pressure-volume changes, one may wish to instill air, aliquot for aliquot of fluid being removed. One may easily detect radiographically as little as 30 c.c. (or less) of air in the pericardium (Fig. 10), but the usual minimum for good demonstration is around 100 to 200 c.c. Subsequently, roentgenograms of the chest reveal the air bubble in the chest, the thickness of the parietal pericardium, and the size of the enclosed heart if enough air is instilled. This can be of considerable clinical value. Not only does it show the level of fluid remaining in the pericardium, but it is known, for example, that tuberculosis of the pericardium is associated with a small heart (Fig. 11), whereas rheumatic pericarditis may be associated with a large heart.[25] Nodular neoplastic metastatic tumors may be seen along the parietal pericardial surface above the air bubble, etc.

With recurrent effusions, or when one wishes to remove as much fluid as possible without haste, or when instillation of cytotoxic drugs may be indicated, placement of a polyethylene catheter in the pericardial sac may be helpful.[21] For this purpose, PE 190 polyethylene tubing may be threaded through a No. 13 or No. 14 gauge thin-walled needle. Other combinations that may be used are: PE 90 tubing with No. 16 thin-walled needle, and PE 50 tubing with No. 18 thin-walled needle.[24] For checking the location of the catheter radiographically when radiopaque

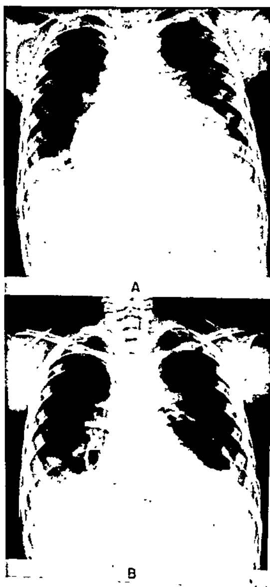


Fig. 11. Diagnostic pneumopericardium in a patient with acute tuberculous pericardial effusion. Note the normal heart size detectable in *B* after the instillation of air into the pericardial sac.

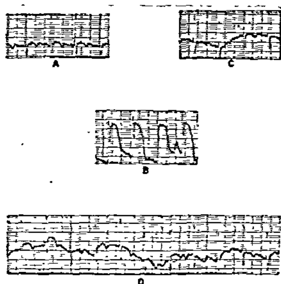


Fig. 9 Electrocardiographic monitoring of pericardial paracentesis. *A*, After needle had penetrated pericardial sac and fluid had been aspirated. *B*, Needle in direct contact with the ventricular myocardium *C*, Needle withdrawn slightly. *D*, Needle barely touching myocardium in first part of this tracing, and then very slightly withdrawn. Consult text for details.

significant arrhythmias, one is able to detect when the needle engages the myocardium. This is of help not only as a warning sign but also in defining the location of the needle and any fluid obtained. When the ventricle is touched by the advancing needle, one observes S-T-segment elevation (Fig. 9) and, occasionally, ventricular premature contractions of the QS configuration. QS premature contractions are characteristic of those produced by the needle when it acts both as an irritant and as an electrode.[24] It should be noted that the important S-T-segment shifts are not detectable in the limb leads. When the needle touches the atrium, P-R-segment elevation and auricular premature contractions (with inverted P waves) may be observed. These electrical changes may be noted even when no perceptible impulse is transmitted to the syringe; thus, it is a valuable guide. It should be remembered, however, that, occasionally, the electrocardiographic signs of myocardial contact may occur when the needle has not penetrated the myocardium, but only indented the parietal pericardium.[24]

For the actual drainage of fluid, one

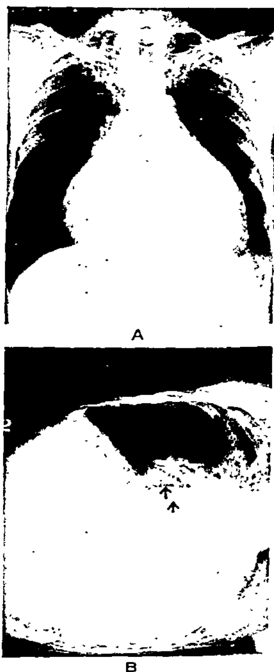


Fig. 10. Combined diagnostic procedure of induced pneumopericardium and intracardiac injection of carbon-dioxide in a patient with tuberculous pericarditis and effusion. *A*, Erect film showing "water-bottle" configuration of the cardiac silhouette. *B*, Left lateral decubitus film, after the injection of 30 c.c. of air into the pericardial sac and with 50 c.c. of carbon dioxide in the right atrium. From above downward, one observes aerated lung, thickened pericardium, air and air-pericardial fluid level (*top arrow*), and the carbon-dioxide bubble (*lower arrow*).

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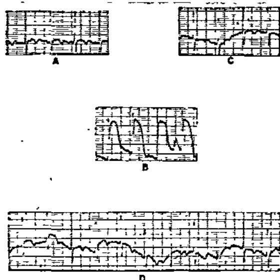


Fig. *9*. Electrocardiographic monitoring of pericardial paracentesis. *A*, After needle had penetrated pericardial sac and fluid had been aspirated. *B*, Needle in direct contact with the ventricular myocardium *C*, Needle withdrawn slightly. *D*, Needle barely touching myocardium in first part of this tracing, and then very slightly withdrawn. Consult text for details.

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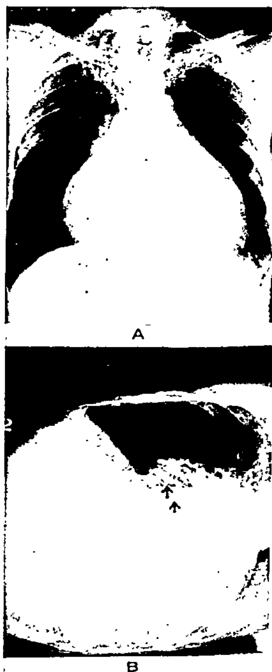


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times polyarthritis or arthralgia. In a few instances of postmyocardial infarction syndrome, I observed the development of hard, indolent nodes on the fingers; these nodes disappeared after about 6 weeks. The concept of autoimmunization has been applied. Serologic studies revealed the presence of antibodies against extract of species-identical myocardium in both the postmyocardial infarction syndrome[6] and the postcardiotomy syndrome.[7] However, it is still undecided whether the serological changes are the cause of the condition or just an attending feature.

The striking therapeutic effect of corticosteroids might also be mentioned in support of allergic etiology. Hormonal therapy, indeed, has a surprising immediate effect when used in adequate dosage. As in rheumatic fever, reduction of the dose or discontinuation of the therapy is followed by rebounds in most cases. An instance of postmyocardial infarction syndrome has been reported[8] in which, during a period of 2 years, withdrawal of steroids produced violent relapses every time; these relapses ranged from fever, chest pain, and pericardial effusion to shock and anuria. Such prolonged duration in spite of the use of steroids seems to speak against a curative effect of the hormones and, rather, to support the view that hormonal therapy suppresses only the toxic and inflammatory reactions without eliminating the cause.[9] Gradual withdrawal of the drug does not appear to change the incidence of rebounds. However, it is usually possible with a small maintenance dose of 15 or 5 mg. per day to prevent relapses and avoid unpleasant side effects of this therapy.

I used Butazolidin in a few instances, with favorable effect, similar to that of hormonal therapy. Its withdrawal was followed by rebounds. Because of the toxic effect of Butazolidin, hormonal therapy is preferable. Aspirin and aminopyrine cause relief of symptoms only in exceptional cases.

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Fatty change in the myocardium of newborn infants

In many babies who die soon after delivery or in the first few days of life there is both clinical[1,2] and postmortem evidence[3] of cardiac failure. Such deaths can be divided broadly into three groups: (1) those due to atelectasis, hyaline membrane disease, or pulmonary hypoplasia; (2) those which result from unavoidable loss of fetal blood in utero, hemolytic disease of newborn infants, or placental insufficiency; and (3) those (few in number) due to congenital heart disease.

The majority of cases fall into the first group, and at postmortem the appearances invariably indicate a terminal right heart failure. This in all probability develops as a result of increased pressure in the pulmonary artery[4,5] due to an atelectasis which may be primary, secondary, or congenital. Moreover, as the pressure in the pulmonary artery rises, fetal circulatory pathways are reopened and, in addition to increasing the load on both sides of the heart, this further aggravates the anoxia.

In the second group it is possible that anoxia frequently of anemic origin affects the fetal heart before delivery, rendering it less able to maintain normal pressures during the first few vital moments of independent existence. Thus, fetal pathways do not entirely close, and conditions similar to those described above reduce even further the cardiac reserve.

In the third group the congenital abnormality itself places an extra load on the heart. The pathways attained vary according to the nature of the abnormality.

It can be seen that in all three groups the terminal cardiac failure is associated with conditions which give rise to anoxia and increased cardiac load. The clinical and postmortem

Some aspects of noninfectious, recurrent, benign pericarditis

Our views as to the incidence of various etiological forms of pericarditis have changed in the past decade, largely because of the recognition of some previously unknown types of pericarditis Whereas in 1953, rheumatic and purulent pericarditis were thought to be the most frequent kinds,[1] lately a group of noninfectious, recurrent, benign types of pericarditis moved to the foreground. This group includes what is called "idiopathic" pericarditis, the postcardiotomy syndrome, traumatic pericarditis, and the postmyocardial infarction syndrome. I suspect that Siegal's benign paroxysmal peritonitis[2] belongs also to this group. These varieties of pericarditis have some features in common. (1) absence of infectious agents, (2) involvement of pericardium, pleura, lungs, and, probably, peritoneum, either simultaneously or in successive stages, (3) an exudate which is frequently hemorrhagic, (4) benign character, (5) severe chest pain, and (6) tendency to frequent recurrences

"Idiopathic" pericarditis is the least well-defined group. This group may be expected to shrink when further study elucidates the etiology of some of the cases and separates them from the "idiopathic" trash basket. Already, it has been shown that about 15 per cent of the cases listed as idiopathic are connected with a Coxsackie virus infection.[3] Some others of the "idiopathic" variety are probably of rheumatic origin, that is, pericarditis which occurs in patients with rheumatic background or in those suffering from chronic rheumatic heart disease. Recently, some instances of "idiopathic" pericarditis were separated under the heading of "coronary pericarditis."[4]

The postcardiotomy syndrome was initially thought to be peculiar to rheumatic heart disease and to represent rheumatic activity It was later observed in patients operated on for congenital heart disease, even when no more than the pericardium was incised. Recently, I observed the postcardiotomy syndrome in 3 patients in whom a cardiac pacemaker had been implanted.

A traumatic form of noninfectious, benign pericarditis was observed in patients whose pericardium had been pierced by bullets or shrapnel fragments (P. Wood), and after accidents in which the heart was not even involved (Mattingly). It is of interest that some instances of "idiopathic" pericarditis occurred shortly after operation on the thyroid gland, cholecystectomy, appendectomy, and hernia and sinus operations. It would seem that these types of traumatic pericarditis are closely related to the postcardiotomy syndrome and probably also to the postmyocardial infarction syndrome in which injury to the heart is due to ischemia rather than trauma.

The term "pericarditis" is a misnomer since, besides the pericardium, other serous membranes as well as the lungs may be involved. In certain stages, pleuritis or peritonitis may predominate. I observed a patient with allergic background who suffered from recurrent pleuritis for 13 years. Then, severe recurrent pericarditis dominated the clinical picture. Likewise, cases of paroxysmal peritonitis were reported[2,5] in which chest pain aggravated by breathing or exudative pleuritis were the sole manifestations for many years, whereas recurrent peritonitis developed in later years.

Relapses are a characteristic feature of the group under discussion and may occur over a period of weeks, months, or years, often with decreasing intensity.

The hemorrhagic character of the exudate has been previously attributed to tuberculosis or carcinoma. This view has to be revised in as much as a stark hemorrhagic exudate has been observed in association with rheumatic pericarditis as well as with various forms of noninfectious pericarditis.

The term "benign" is least suitable for defining an etiological group of types of pericarditis since the benign character cannot be recognized in the initial stages but, rather, is diagnosed in retrospect. What is originally thought to be benign may later turn out to be constrictive pericarditis. Moreover, in a few instances of postmyocardial infarction syndrome, sudden death has been observed in the acute stage, which raises some doubt whether this condition is invariably of benign character.

The etiology of the types of pericarditis under discussion is unknown A search for infectious agents in the blood, sputum, and pericardial, pleural, and peritoneal exudates is unsuccessful. Antibiotics do not influence the course. It is well known that pericarditis, pleurisy, and pneumonitis may be associated with allergic conditions. Hence, sensitization has been suspected to be the cause of noninfectious pericarditis. Some clinical observations seem to support this view. Not infrequently, the patients have an allergic personal or family background; eosinophilia is often present; there is some-

the horns, or to attack the dilemma by showing *that the major premises are false.* This is the most promising approach in the proposed situation. Taking the first premise—that adequate digitalis results in intoxication—one should remember that even though this may be true at one time, it may not be true at all times for a given patient. Circumstances, such as heart failure, electrolyte imbalance, and respiratory failure, may temporarily alter the response to digitalis. If these can be corrected without digitalis, one may then find that the therapeutic and toxic doses of digitalis no longer overlap. If heart failure is treated by other means, digitalis may then be used to prevent its recurrence. Others have attacked the first premise by attempting to demonstrate that certain digitalis preparations have wider margins of safety. This proposition, vigorously defended by some, has not won general acceptance.

Attacking the second premise of the dilemma means permanently treating the heart disease by means other than the use of digitalis. Heart failure and digitalis have become so inseparably linked in the minds of many that we may forget that digitalis is not the only answer to the treatment of heart disease; in many cases it is not even a very good one. Valvular heart disease, pulmonary heart disease, and congenital heart disease, for example, respond rather unsatisfactorily to digitalis. Acute pulmonary edema will usually respond well to tourniquets, reduction of anxiety and respiratory *effort, defoaming agents, and positive pressure* breathing. For the treatment of chronic heart failure, restriction of activity, a low-salt diet, diuretics, treatment of metabolic disturbances, treatment of respiratory failure, appropriate heart surgery, and reduction of hypertension may render digitalis relatively unimportant.

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Use of computers in ECG interpretation

The electrocardiogram was selected for a pilot project *in electronic data processing (EDP) of* cardiovascular information. The electrical heart signals are repetitive and, therefore, well suited for mathematical analysis. The first problem which needed to be solved was the selection of appropriate ECG leads for EDP. The 12 leads which are gener*ally used in* clinical electrocardiography would require 12 input channels for recording since the acquisition of simultaneous data is desirable in order to maintain phase relationships. Decreasing the large expense for recording equipment by selecting a few leads out of 12 must necessarily be arbitrary because no quantitative studies are known for determination of the information content of single leads. It was found, however, that a large part of the standard 12-lead information is redundant.[1] Since ECG information is derived to a great extent from its spatial characteristics, simultaneous recording of 3 orthogonal leads appears to be a rational choice. Both scalar and vectorial analysis can be performed on such records. In a previous study[1] it was found that the clinical information contained in 12-lead records is also available from orthogonal 3-lead tracings. This finding could be corroborated later on the basis of several thousand orthogonal records. Thus, a reduction of data by a factor of 4:1 appears to be possible without loss of clinical information. Such reduction of data is most important in any EDP project because large amounts of data *may exceed computer capacities.*

Magnetic tape recording and storage appeared to be best suited for EDP because reproduction of the original ECG analogue voltages is necessary *regardless of whether analogue or digital computers* are considered for data processing. The greater flexibility of digital computers was considered to be advantageous in the development phase of the project. Once a set of optimal analytical procedures has been determined a special-purpose analogue computer may be *designed* for automatic ECG analysis. The choice of a digital computer made it necessary to obtain an automatic analogue-to-digital converter[2] in order to make the original analogue information compatible with digital computers. Voltages of each lead are measured at intervals of 1 millisecond and re-recorded *in numerical form* on digital magnetic tape. Consequently, they are fed directly into a commercially available digital computer (IBM 7090) for data processing and analysis.

Since the ECG consists of several distinct wave forms with different electrophysiologic significance, a first computer program had to be developed for automatic recognition of the beginning and the end of these waves.[3] A digital filter of the moving average type was applied first in order to eliminate A.C. interference, muscle tremor, and other artifacts. Consequently, the spatial velocity was determined on the basis of the 3 orthogonal components. It was found that a critical velocity limit of 3 μV/msec. was not exceeded during T-P, P-R, and S-T segments. The point at which this critical value is reached indicates the beginning of a wave. Values below this level are found at the end of waves. This computer program led to measurements

cardiac failure find confirmation in a recent paper by Scott,[3] who has shown that in these conditions stainable fat appears in the myocardium but, apart from a few exceptions, is not seen in stillbirths or in neonatal deaths, in which there is no evidence of cardiac failure When present, the fatty change tended to occur earlier in the right heart, but in older babies both ventricles were equally involved. The amount of fat present appeared to be related to the duration of cardiac stress, and this was especially noticeable in those in whom death was due to hyaline membrane disease.

Cardiac metabolism was not studied in any great detail but several interesting points did arise. Obviously, some metabolic derangement was present. Normally, glucose, lactate, pyruvate, and nonesterified fatty acids are the main sources of energy available to the heart. For each of these there is a definite threshold of extraction In the majority this is near zero, but in the case of glucose the threshold is much higher, 59 ± 6 mg. per cent.[6] Levels of blood sugar in the newborn infant are frequently below this level, especially in the case of prematurity, in which instance the custom is to keep the baby without food for the first 2 days. Thus, it is not surprising that under these circumstances the myocardium should have to derive most of its energy from the oxidation of fatty acids. This is certainly in line with recent research.[7] It is more difficult, however, to explain why the fat should appear in stainable form. One can only postulate that with the increasing effort and progressive anoxia some upset in catabolism must occur and, although the fat is available, it can no longer be utilized adequately.

The deposition of glycogen in these hearts was also studied. Even though it was realized that no great stress could be placed on a histochemical method such as this, it was interesting to note that gross depletion of glycogen was usually found only in those hearts which showed the most marked fatty change. In other words, the reserve of glycogen would appear to be called upon only as a last emergency, a finding which agrees with the experimental work of Fletcher and Waters.[8]

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A therapeutic dilemma

The conditions of modern life being what they are, the term "dilemma" seems to stare at us with increasing frequency. A dilemma is a type of impasse in which a choice must be made between two equally undesirable courses of action. The situation in which the therapeutic and toxic doses of digitalis overlap presents such a dilemma. It may be formally stated as follows: *If adequate digitalis is given, the patient will develop digitalis intoxication; if digitalis is withheld, heart failure will result.*

Formal logic suggests three solutions for the individual impaled on the horns of a dilemma.[1] The first is escape through the horns. This implies finding a third course of action, and in terms of our particular problem would mean an alternative to giving digitalis or not giving digitalis. Since these two courses allow for no others, this approach must be abandoned. The second approach is to ride one of the horns, or to create the counterdilemma. Ruby[1] gives the following example. A young man contemplating marriage may reason thus: "If I get married I will be forced to assume grave responsibilities and worries; on the other hand, if I remain single I will be lonely." Creating the counterdilemma would be to point out that he is *actually faced with two desirable choices:* either he can marry, in which case he will not be lonely, or he can remain single and carefree. In terms of our therapeutic dilemma, we can state that, one can give digitalis, in which case the patient, although intoxicated, at least will be out of heart failure, or one can withhold digitalis and avoid digitalis intoxication, although a degree of heart failure must be accepted. Few clinicians would be consoled by such a counterdilemma.

The third solution is to take the dilemma by

Book reviews

ANATOMY OF THE CORONARY ARTERIES. By Thomas N. James, M.D., F.A.C.P., Chairman, Section on Cardiovascular Research, Henry Ford Hospital, Detroit, Mich. New York, 1961, Paul B. Hoeber, Inc., 211 pages, 136 illustrations. Price $18.

The author has made a thorough study of the gross anatomy of the normal distribution of the coronary arteries in man by use of the injection-corrosion technique. The material is presented in an orderly and understandable fashion. The book is generously illustrated with sketches and photographs, many of them in color. The written text is well organized and concise. The book has been published on excellent paper, and the quality of the photographic reproductions is superb.

This book is a distinct contribution and a definitive treatise on the gross anatomy of the coronary arteries in man, and it can be recommended wholeheartedly to all those interested in this subject.

SYMPOSIUM ON ANGIOTENSIN (American Heart Association Monograph No. 3). Edited by J. Edwin Wood, M.D., and Raymond P. Ahlquist, Ph.D. Proceedings of a symposium held May 13, 1961, in Augusta, Ga., and supported by the Medical College of Georgia Foundation through a grant from CIBA Pharmaceutical Products, Inc. New York, 1962, American Heart Association, 270 pages. Price $2.50.

This is a compendium of the papers presented at a symposium on angiotensin The collected papers are very good and should interest those who wish to learn about an interesting and potent polypeptide. The papers do not review the subject completely, but do so fairly well for the average person who wishes to acquaint himself with a rapidly advancing subject. This monograph, Number Three of the American Heart Association, was published as a period supplement to *Circulation* in January, 1962. Although the symposium was held on May 13, 1961, and represents data which are now over a year old, much of the data are fundamental and still quite valuable. This is a good monograph

BLOOD VESSELS AND CIRCULATION. Advances in Biology of Skin, Vol. II (Proceedings of the Brown University Symposium on the Biology of the Skin, 1960). Edited by William Montagna and Richard A. Ellis, Arnold Biological Laboratory, Brown University, Providence, R. I. New York, 1961, Pergamon Press, 156 pages. Price $10

The material in this book is based on the proceedings of the Brown University Symposium, "The Biology of Skin. The Blood Vessels and Circulation of Blood in the Skin" The symposium was held on Jan. 30 and 31, 1960

The book contains nine chapters: I. Cutaneous Vascular Patterns (R. K. Winkleman). II. Vascular Patterns of the Skin (R. A. Ellis). III. X-Ray Projection Microscopy of the Skin (R. L. de C. H. Saunders). IV. The Fine Structure of Cutaneous Capillaries (G. F. Odland). V. The Innervation of Cutaneous Blood Vessels (G. Weddell). VI. Capillary Microscopy in Normal and Diseased Human Skin (M. J. Davies and J. C. Lawler). VII. Effects of Heat on Cutaneous Blood Flow (A. B. Hertzman). VIII. Special Features of the Circulation of the Skin (A. C. Burton). IX. The Blood Supply of Tumors (F. Urbach).

The material presented in this book touches on selected aspects of the anatomy, physiology, and pathology of the cutaneous vessels. As indicated by the editors, this collection of works is not intended to be a comprehensive survey of cutaneous vascular investigations, and, of necessity, many areas are omitted in the presentations. Nevertheless, the subjects that are covered are presented in a clear and concise manner. Emphasis is laid on specific methods used in the study of the cutaneous blood vessels and the circulation. It is obvious that although many of these methods are excellent, they are only just beginning to bear fruit. Much needs to be done, but the future looks bright.

The information provided in this small book is oriented from the standpoint of the basic investigator, but it should hold much interest for all those engaged in the study of the peripheral vascular circulation.

THE NATURE OF ESSENTIAL HYPERTENSION. By Sir George Pickering, M D., F.R.C.P., F.R.S., Regius Professor of Medicine and Student of Christ Church, Oxford University, London. New York, 1961, Grune & Stratton, Inc., 151 pages. Price $4.

In this small book, Sir George Pickering has set down his ideas concerning the etiology and pathogenesis of what, in our ignorance, we call *essential hypertension*. Briefly stated, his hypothesis is that arterial pressure is inherited polygenically as a graded characteristic, that elevated arterial pressure begets elevated arterial pressure, and that the degree of elevation is dependent not only on inherited factors but also on environmental influences. The implication of this proposal is that essential hypertension represents a quantitative, not a qualitative, deviation from the norm.

The first chapters of the book deal with a discussion of the old ideas of essential hypertension, which has been considered by many as a qualitative abnormality; this is in direct opposition to Dr. Pickering's new idea that it is a quantitative change. The next several chapters carefully present the genetic and environmental data that have led Pickering and his colleagues to conclude that arterial pressure is, like heig a graded inheritance. Here he systemat

of wave durations and intervals in between them which are essential for any ECG analysis.

A further program led to determinations of the spatial ventricular gradient on the basis of time integrals of scalar leads.[4] The components of SVĜ, namely, SÂQRS and SÂT, were also determined separately. Although the ventricular gradient had been proposed as an analytical criterion many years ago, its use has never become widespread because manual determinations are not only very time-consuming but also relatively inaccurate.

An additional program led to determinations of Burger's polar vector and Eigenvectors. On the basis of Schellong's observation that normal QRS loops form almost perfect planes, the suggestion was made to use a vector perpendicular to this plane in order to define its spatial orientation. Three Eigenvectors form an orthogonal reference frame which defines the length and width of the loop and deviations from the QRS plane. This reference frame, which is based on the spatial orientation of loops rather than on body axes, becomes independent of interindividual QRS variations due to body build and other extraneous factors. Polar vectors and Eigenvectors are obtained not only for QRS loops but also for P and T loops.

An automatic XY plotting device of the digital computer was used for the representation of time-based graphs of spatial velocity, spatial magnitude, and orientation in terms of azimuth and elevation angles. In addition, print-outs with spatial magnitude and orientation were obtained for instantaneous vectors. These were determined at 0.01-second intervals during QRS, and at 0.02-second intervals during S-T. In order to eliminate the variability in normal QRS duration this complex was also divided in time into 8 equal parts, and instantaneous vectors were obtained for these subdivisions. The characteristics of the S-T segment were defined in terms of slope and curvature.

A final program consisted of measurements of wave durations and amplitudes, such as Q, R, and S, for each scalar component. In addition, Q/R and R/S ratios were printed out.

The described programs were tested successfully on approximately 2,000 records. A normal control was obtained from 500 "normal" subjects. Tests samples with known abnormalities were compared with this control. Classifications of unknown records were then obtained on the basis of frequency-density distribution functions of the various ranges, using a likelihood ratio test. Thus, a differential diagnosis is obtained for each case, with a print-out of probabilities for each diagnostic category.

The described programs require approximately 5 seconds of computation time for one record. The various analytical procedures are being evaluated at present for their diagnostic usefulness, in order to arrive at an optimal set of diagnostic criteria. In addition, programs for the analysis of arrhythmias are being developed. From the experience gained it appears that automatic ECG analysis represents a powerful tool in the analysis of individual records and in the handling of mass data.

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authors of simple books cannot afford to be quite as simple as this. This book could easily be a chapter in a general textbook on medicine, and, although it would be unfair to damn it, it is equally difficult to praise it.

FAINTING. PHYSIOLOGICAL AND PSYCHOLOGICAL CONSIDERATIONS. By George L. Engel, M.D., Professor of Psychiatry, and Associate Professor of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Second edition, Springfield, Ill., 1962, Charles C Thomas, Publisher, 196 pages. Price $7.50.

Dr. Engel starts his excellent monograph with the statement that probably no clinical symptom is as well known among lay people as fainting. Throughout much of the book he uses the word *syncope* as a synonym. He derives syncope from the Greek, via *Webster's New International Dictionary*, to mean "a cutting short." Liddell and Scott's *Oxford Greek English Lexicon*, by contrast, gives "falling down in a swoon, sudden loss of strength," as used by Aretaeus and Galen. The introductory chapter closes with a fine classification of fainting. The second and third chapters deal with circulatory and cardiac mechanisms, important factors in most instances of fainting. The two main types, i.e., vasodepressor and postural hypotension, are described well, as are also those varieties associated with cardiac disorders: cardiac standstill, transient and paroxysmal heart block, paroxysmal tachycardia, coronary insufficiency, and myocardial infarction. In the fourth chapter, Dr. Engel describes the sundry respiratory disorders associated with fainting, which include hyperventilation, the Valsalva maneuver, and the interesting cough syncope. The next two chapters concern themselves with neuropsychiatric disorders, which are discussed with particular skill. The book closes with chapters on the incidence and diagnosis of fainting. The monograph is recommended as a good survey of current knowledge of a common problem.

HEART, KIDNEY AND ELECTROLYTES. Edited by Charles K. Friedberg, M.D., Cardiologist and Attending Physician for Cardiology, The Mount Sinai Hospital, New York, and Associate Professor of Medicine, Columbia University, New York. New York, 1962, Grune & Stratton, Inc., 420 pages. Price $11.75.

This book is a reprinted series of papers by a group of distinguished investigators from the Symposium on Heart, Kidney and Electrolytes, published in the journal, *Progress in Cardiovascular Diseases*. There are 21 articles covering the various aspects of fluid and electrolyte regulation and its disturbances in diseases of the circulation and of the kidneys. Each article is followed by 50 to 100 references. The preface describes the articles as authoritative, lucid, and informative. They are certainly authoritative and informative, but such subjects as membrane transport and counter systems of concentration cannot be explained simply, and many readers will not find these chapters to be lucid.

There is an emphasis throughout the book on interpretation of clinical phenomena in the light of known experimental data, and this is a healthy corrective to the more glib and unsupported hypotheses with which most clinicians are familiar. In many instances the chapters overlap in their subject material (for instance, there are three papers which discuss hyponatremia in cardiac failure), but there is sufficient agreement upon the main principles so that this serves to help rather than confuse the reader.

The book can be strongly recommended to all who have an academic interest in fluid and electrolyte problems.

deals with Dr. Robert Platt's contention that essential hypertension is inherited as a manifestation of a single gene behaving as a Mendelian dominant. (This is the contention which has resulted in the famous polemic for which *Lancet* is the official organ.) There follows a discussion of the environmental factors—to my mind, the weakest section of the book. Then comes a section on pathogenesis in which vascular disease associated with hypertension is attributed to an elevated arterial pressure. Finally, there is a restatement of the idea that essential hypertension represents a quantitative, not a qualitative deviation from the norm, a discussion of its criticisms, of its truth, its usefulness, and its therapeutic implications. Throughout the book there is much on the importance of ideas and on the importance of this particular idea because it represents "a qualitative" deviation from some present-day concepts. I wonder whether the emphasis on this idea is not a bit exaggerated, for it seems to me that inherited disorders are often quantitative deviations from the norm.

This is a provocative book, as are most things that Sir George writes. For those who have had little experience in the field of genetic and statistical methods the first section may be hard going, but the information gained will be worth the struggle.

Arteriography. By David Sutton, M.D., M.R.C.P., F.F.R., D.M.R.D.; Consultant Radiologist, St. Mary's Hospital, London; Consultant Radiologist, Maida Vale Hospital (The National Hospitals for Nervous Diseases), London. Teacher in Radiology, St. Mary's Hospital Medical School, University of London. Teacher in Radiology, Institute of Neurology, Postgraduate Medical Federation, University of London. With a foreword by Rohan Williams, M.D., F.R.C.P., F.R.C.S., F.F.R., F.C.R.A. (Hon.), President of the Faculty of Radiologists. Edinburgh and London, 1962, E. & S. Livingstone Ltd., Baltimore, Williams & Wilkins Company, 318 pages, 284 figures. Price $13.50.

This well-organized monograph is based on a personal experience, over a period of 14 years, of over 10,000 percutaneous arteriograms of most of the arterial systems of the human body. It is likely that very few individuals have had experience of such breadth and depth in the general field of arteriography.

Part I has several chapters on historical background, technique and instrumentation, principles of radiography, contrast media, and complications. Part II has chapters on clinical aspects and arteriography of specific regions.

The use of needles with a short bevel is stressed; this prevents intramural and perivascular injections. Local anesthesia is preferred in most instances because of the greater number of complications, including death, with general anesthesia.

Very sound and practical advice is given in regard to radiographic equipment and technique. Methods of protection for patient and operator are described. Tri-iodated contrast agents are preferred; 60 per cent Urografin or Renografin is about equivalent in iodine content to 45 per cent Hypaque. It is advisable to keep the quantity injected as low as possible. The complications, which are fully discussed, may be prevented by meticulous application of technique and the use of small doses of contrast medium.

The investigation of vascular lesions and tumors, or suspected tumors, is described for various regions of the body. The vascular lesions include thrombosis, embolus, aneurysm, arteriovenous malformation, arteriovenous fistula, congenital anomalies, and spasm. Many arteriograms are reproduced with clinical notes from the author's personal experience, which adds considerable value to the monograph.

The description of collateral circulation after occlusions of the aorta and iliac arteries is meager. Anatomic background is given only in the section on intracranial arteriography. It is perhaps a question of judgment whether these data should have been included.

There is one final chapter on the arteriography of tumors which stresses that, whereas highly malignant tumors usually have an abnormal vascular supply, a few benign tumors and inflammatory processes have also shown this type of finding. Considerable judgment has to be exercised when interpretation of arteriograms is made from the standpoint of whether malignancy is present.

The arteriography of the head and neck was intended to be brief, and not as a complete analysis of arteriography for the neurosurgeon or neuroradiologist. However, it does have valuable basic information for the general arteriographer.

This monograph is lucidly written and will be of value for radiologists, internists, and surgeons interested in the general field of vascular disease.

A Guide to Cardiology. By J. C. Leonard, M.D., M.R.C.P., Senior Medical Registrar, United Manchester Hospitals, and Manchester Regional Hospital Board, and E. G. Galea, M.B., M.R.C.P., M.R.A.C.P., Cardiologist, Brisbane Children's Hospital. Baltimore, 1961, The Williams & Wilkins Company, 267 pages. Price $6.50.

This book is written for students and recently qualified practitioners. It is a small book and written throughout in very simple terms. The print is large and the illustration is generous. This book will be of value to the student who wishes to know just enough to pass his final examination or reach general registration standard, but it is hardly fare for the more curious and intelligent student. There is a rather traditional outlook throughout the book, and the "atrium" remains the "auricle." Modern knowledge of hemodynamics, which often clarifies rather than complicates, is not employed enough in exposition.

Starling's law is mentioned (in capital letters) as applicable to the intact and diseased subject with a naïveté which is a little disturbing. The

American Heart Journal

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Editorial

Cardiology without tears

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The rapid and continuous increase in complicated instrumental aids to diagnosis tends, as years go by, to blind the physician to the details of his own clinical technique. There are a number of simple measures which will increase the cardiologist's efficiency and decrease the patient's discomfort.

The consulting room should be warm and quiet, and not too frighteningly clinical in decoration. An oblique light is an advantage, for when standing in it the patient can be slowly rotated so as to throw into relief, like the mountains bordering the shadow on the moon, such phenomena as aneurysmal pulsation, systolic recession, and the pulsating collateral arteries of coarctation of the aorta. Easy shading and darkening of the consulting room is necessary if a simple x-ray screening unit forms part of the clinical armamentarium.

The examination couch should be broad and tall, to save the physician from unnecessary stooping, and to make easy for the patient that degree of relaxation which helps physical examination and prevents muscular tremor from distorting the electrocardiogram. A good breadth for the couch is 30 inches, and a good height is 32 inches. The length should be adequate, say, 6 feet 6 inches, and the adjustable head and shoulder raising must be both easy and sufficient.

Received for publication Feb. 21, 1962.

In addition to the usual blankets and pillows the preliminary use of an electric blanket is appreciated in cold weather.

History taking, that part of the examination from which the experienced physician can learn most, should never be delegated to a junior or to a nurse. The more personal the examination from start to finish, the greater will be the chance of extracting from a shy patient relevant symptoms, both physical and psychological in nature.

Each physician should plan the layout of his own clinical case sheet. It is wise to have this printed. It should be comprehensive, so that even a tired doctor will not for that cause omit some relevant item. A good plan is to use a single folder. In addition to personal particulars, such as name, age, and address, there are laid out on the outside page three sections dealing with Past History, Family History, and Present Symptoms. These are subdivided into headings; for example, in the section on Past History are Acute Rheumatism, Chorea, Scarlet Fever, Syphilis, and Other Diseases. Down the left-hand margin, in order, are cardiac symptoms, such as Dyspnea, Orthopnea, Sighing, Constriction, Pain, etc., and general symptoms, such as Dyspepsia, Bowel Action, Frequency of Micturition, and so on. The center of the page is blank, and here is recorded the detailed case history. Thus,

Announcements

The University of Texas Postgraduate School of Medicine is pleased to announce a clinical symposium on THE PRACTICAL TREATMENT OF HYPERTENSION, scheduled for Thursday, Friday, and Saturday, Sept. 20, 21, and 22, 1962. The symposium will be held in the auditorium of The University of Texas M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, Tex.

The program will include a number of outstanding guest speakers who will discuss hypertension as follows: Theories and concepts regarding etiology, metabolic observations, hemodynamics, natural history, indications for treatment, various therapeutic agents, and surgical procedures. Emphasis will be placed on the medical-surgical treatment of essential hypertension and curable forms of secondary hypertension. There will be no tuition fee.

For further information write Office of the Dean, The University of Texas Postgraduate School of Medicine, 102 Jesse Jones Library Building, Texas Medical Center, Houston 25, Texas.

CARDIOVASCULAR SURGERY will be the subject of one of the ten postgraduate courses offered by the American College of Surgeons during its 1962 Clinical Congress in Atlantic City, New Jersey. George H. A. Clowes, Jr., M.D., Cleveland, is chairman of the course, which will be conducted Oct. 16-19, 1962, from 8.30 to 11.30 A.M. each day. Daily subjects and moderators will be: October 16, Occlusive Disease of the Peripheral Arteries, E. Stanley Crawford, M.D., Houston; October 17, Hypertension and Vasospastic Diseases, Fiorindo A. Simeone, M.D., Cleveland; October 18, Congenital Heart Disease, Frank Gerbode, M.D., San Francisco, and October 19, Acquired Valvular Disease and Management of the Cardiac Surgical Patient, C. Walton Lillehei, M.D., Minneapolis.

Fee for the course is $10. For further information write: William E. Adams, M.D., Secretary, American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

A course in INTERPRETATION OF COMPLEX ARRHYTHMIAS will be given at Michael Reese Hospital and Medical Center by Louis N. Katz, M.D., Richard Langendorf, M.D., and Alfred Pick, M.D. *This is an advanced course intended only for experienced electrocardiographers.* The class will meet daily from 9.00 A.M. to 5.00 P.M., Dec. 3-8, 1962.

Further information and a copy of the lecture schedule may be obtained from the Secretary, Cardiovascular Institute, Michael Reese Hospital and Medical Center, Chicago 16, Ill.

An International Research Conference on FAT AS A TISSUE will be held on Friday and Saturday, Nov. 2 and 3, 1962, at the Lankenau Hospital, Philadelphia 51, Pa.

A seminar on THE ORIGIN AND SIGNIFICANCE OF THE T WAVE OF THE ELECTROCARDIOGRAM AND THE VENTRICULAR GRADIENT will be held in Burlington, Vermont, on Saturday, September 29, and Sunday, September 30, 1962.

Included among the guest speakers are Dr. John S. LaDue, Dr. E. W. Reynolds, Jr., Dr. R. H. Wasserburger, and Dr. Paul N. Yu.

The seminar is sponsored by the Vermont Heart Association and the University of Vermont College of Medicine. It is open to all interested persons.

Additional information may be obtained from: Eugene Lepeschkin, M.D., Division of Experimental Medicine, University of Vermont College of Medicine, Burlington, Vt.

Erratum

In the article entitled, "The Electrical Field Produced by the Eccentric Current Dipole in the Nonhomogeneous Volume Conductor," by Robert H. Bayley, M.D., and Paul M. Berry, M.A., which appeared in the June, 1962, issue of the Journal, the following corrections are necessary: On page 815, in the second last line, B_n should be replaced by β_n. On page 817, at the end of Equation (1), $0 \leq r \leq R$ should read $0 \leq r \leq R_1$. On page 818, at the end of Equation (4), $R_2 \leq r < R_3$ should read $R_2 \leq r \leq R_3$; and the numerator in the second fraction, A_n, which reads $p_2\alpha_n + p_2\beta_n$ should read $p_2\alpha_n - p_2\beta_n$. On page 819, Equations (1), (2), and (3) should be renumbered (15), (16), and (17), respectively.

Clinical communications

Demonstration of collateral circulation to the lungs with angiocardiographic studies in congenital heart disease

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It has been shown repeatedly that the bronchial arteries may enlarge enormously with obstruction of the pulmonary circulation, as in tetralogy of Fallot,[1] and to a lesser extent with parenchymal diseases of the lung, such as bronchiectasis and tuberculosis.[2-4] This enlargement has also been observed after the occlusion of the branches of the pulmonary artery either by experimental ligation or by embolism.[5-7] The phenomenon has been demonstrated by bronchovascular casts, microscopic examination, postmortem angiographic studies in human material, and in live dogs by selective angiography.[8,9]

Whether these bronchial arteries anastomose directly with the pulmonary arteries has been the subject of much controversy. Miller,[10] in his earlier experiments with dogs, stated that precapillary anastomoses did not exist in normal subjects. However, Brause,[11] Marchand,[12] and Latarget[13] proved by postmortem anatomic studies that bronchopulmonary arterial anastomoses exist, even in normal human lungs.

Physiologic studies in patients[14] and in animals[15] have demonstrated that this collateral circulation was able to participate in gas exchange, and that it, therefore, must reach the alveolar capillaries. Angiocardiographic studies have given indirect evidence that the collateral circulation reaches the pulmonary artery.[16-18] Contrast material in the pulmonary arteries failed to enter diseased areas of the lung after intravenous injections. Liebow and associates[17] concluded that this represented flow of nonopacified blood from systemic collaterals into the pulmonary arteries, causing the opacified output of the right side of the heart to be directed away from the diseased areas into the undamaged parenchyma. Subsequently, Alley and associates[19] confirmed Liebow's inference; they opacified the left pulmonary artery by injecting contrast material into the aorta of a pa-

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a full clinical picture is completed, symptoms absent being crossed out, and those present, and not otherwise recorded, being ticked or underlined. Useful abbreviations can be added, for instance, Orthopnea 4, underlined, means present and four pillows needed. Frequency, $\frac{X}{3}$, means micturition normal by day but three times at night.

The left inside page, headed Present Condition, deals with the physical examination. Here again, the important facts are printed, in logical sequence. Above are the headings Dyspnea, Orthopnea, Pallor, etc., and next are Rate, Rhythm, Blood Pressure, State of Arteries, Veins, and Retinae. Lower down come, Inspection, Apex Beat, Thrills, Heart Sounds, Murmurs, and so on. The sections on lungs and abdominal organs complete that page.

On the opposite leaf are "boxes" for notes on the electrocardiogram, on radioscopy, and, finally, beneath one another, spaces for diagnosis, prognosis, and treatment.

The completed case sheets are used as folders, each containing letters, hematological and other reports, and copies of the electrocardiograms.

They are stored alphabetically, filed at the end of the year, and carried forward annually if the patient is seen at such intervals.

Examination. Examination should be made with the patient first standing, and then lying down. The lungs can best be examined when the patient is standing, and in this position the aortic murmurs may be most easily heard. Mitral murmurs are louder in the recumbent and left lateral positions: vasomotor instability and postural hypotension require investigation in both positions.

The Master three-step stool, so useful in diagnosing cardiac ischemia, provides also an easy ascent to the higher couch.

The dual-purpose stethoscope is best, for high-frequency murmurs, like the aortic diastolic, are most easily heard through the diaphragm, and the low-frequency mitral diastolic bruits through the bell.

The blood pressure is best taken, contrary to usual practice, with the cuff so applied that the rubber tubes run upward toward the shoulder. This leaves the antecubital fossa free for the stethoscope, and places the sphygmomanometer in a position on, near to, or beside the pillow, and away from the eyes of an inquisitive patient.

The most efficient type of ophthalmoscope is that fitted with a 12-volt and 12-watt bulb, and run, if necessary, through a transformer, direct from the main supply. Vision of the retina is easier and better than with the battery type.

A direct-writing electrocardiograph is the most satisfactory for routine clinical work, for the leads can be varied and added to according to what is found at the time.

Suction electrodes for the limbs, if designed for this use, save much time and trouble, but they need periodic and careful cleaning.

A simple x-ray screening unit with wide, fixed screen and a tube movable in both directions, and with good diaphragms, is an invaluable means of measuring accurately the size of the heart. With the technique developed and used by me[1] for 30 years, the size of a heart can be accurately measured in a few minutes and followed from year to year. It can be shown to remain stationary, to have begun to enlarge, or, as in treated myxedema or ligated ductus arteriosus, even to have shrunk.

If a woolen shawl is hung from clips before the screen, the patient can be spared the clammy kiss of this on the bare skin.

The foregoing details of technique are the result of long clinical experience, and have proved both of help to the physician and of comfort to the patient.

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Fig. 1. Film 3: ½ second after Film 2. Right pulmonary and bronchial arteries are opacified.

main pulmonary artery did not fill. Fig 1 demonstrates the sequence of filling of the pulmonary arteries, better seen on the right side. The first film reveals no evidence whatsoever of the right pulmonary artery. The second film, one sixth of a second later, shows contrast material in the bronchial arteries, and in the third film the right pulmonary artery is opacified.

The infant required gavage feeding and continued to have frequent hypoxic spells, which were treated with knee-chest positioning and morphine. There was no improvement in either cyanosis or dyspnea while the child was in oxygen. A shunt procedure was scheduled for the day after the angiocardiography, but death followed a severe spell of hypoxia.

Autopsy confirmed the angiocardiographic diagnosis. The ventricular septal defect was large and the atrial communication was a foramen ovale. The duplicated aortic arch on the left terminated in a ductus arteriosus; the terminal 1 centimeter of the ductus was not patent and could not be opened with probing. The pulmonary valve was absolutely atretic, although the main pulmonary artery and its peripheral branches were well developed and patent. The bronchial arteries were markedly enlarged (Fig. 2) and joined the pulmonary arteries quite near the hilum

In conclusion, the contrast material in the major branches of the pulmonary artery could have entered only by collateral circulation through the bronchial arteries, since both the pulmonary valve and the ductus arteriosus were closed.

Case 2. D W., a 13-year-old girl, was hospitalized for angiocardiographic study. When she was 6 weeks old, cyanosis had become definite and fluoroscopy showed situs inversus. Since that time, she had had recurrent pneumonia. When she was 6 years old, an exploratory thoracotomy was undertaken at another hospital; the pulmonary artery could not be found, although the search had to be curtailed by a deteriorating condition. After the operation, she had a reasonably stable course. Notching of the ribs developed on the right side (Fig. 3), giving evidence of considerable collateral flow on the side on which the thoracotomy had been performed, although the subclavian artery was not touched at the time of operation. She was able to attend school between infections but continued to have marked cyanosis and fatigue.

Physical examination revealed a very thin, small, cyanotic girl who had marked clubbing of the fingers and toes. The lungs were clear to percussion and auscultation. The cardiac impulse was maximal at the right lower sternal border. The first heart sound was slightly accentuated, the second sound was maximal at the second right intercostal space and was single. There was a short, soft, systolic murmur which was maximal at the third right intercostal space. The liver was not enlarged and appeared to be on the left side. The spleen was not palpable.

The hematocrit was 71 per cent. The electrocardiogram showed a P vector which was characteristic of dextrocardia. The QRS vector was slightly to the left and strongly superior and posterior, not characteristic of hypertrophy of either ventricle in ordinary dextrocardia. The QRS-T angle was wide. Radiologic examination revealed dextrocardia with marked decrease in the pulmonary vascular markings, and the presence of notching of the ribs on the right side. Sinus radiograms were normal. Selective biplane angiocardiography revealed a single large ventricular chamber and a diminutive second ventricle just below the common outflow tract. The mitral valve was not demonstrated, and mitral



Fig. 2. Case 1. Aorta, demonstrating exceptionally large bronchial arteries.



Fig. 1 Case 1. Left atrial injection, frontal projection. Film 1: Left atrial appendage, left ventricle, and aorta are filled. The major aortic arch descends on the patient's right A second arch (*arrow*) is on the left, ending in a closed ductus arteriosus No opacification of the right hilum has occurred

tient with severe suppurative disease of the left lung. The angiographs were not published, however. Nordenström,[8] using angiographic studies in chronic animal preparations, published remarkably clear proof of filling of ligated pulmonary arteries beyond the ligation, via bronchial arteries.

The sites of the anastomoses between collaterals and pulmonary artery have been described by Liebow and associates.[17] In cyanotic congenital heart disease associated with obstruction of the proximal portion of the pulmonary circulation, these collaterals connect centrally, close to the hilum. In parenchymal lung disease, these communications occur more peripherally. The sequence and mechanism of the development of these communications has been described by Weibel[20] in a complete study of the development of the collateral circulation in rat lung after ligation of one pulmonary artery.

We have recently observed 3 patients with cyanotic congenital heart disease who demonstrated three aspects of collateral circulation. Filling of the pulmonary arteries via central bronchial and peripheral collaterals, respectively, was demonstrated during life by angiocardiographic studies in the first two patients. The third patient, who demonstrated marked enlargement of the bronchial arteries without subsequent opacification of the pulmonary artery, had obliterative pulmonary hypertension.

Case reports

Case 1. E. G., a 3-month-old white female infant, was hospitalized because of severe cyanosis since birth, tachypnea, difficulty in feeding, and physical retardation. The mother described frequent episodes of rapid labored breathing, increased cyanosis, and exhaustion.

Physical examination revealed a markedly cyanotic, thin infant who was in moderate respiratory distress. The chest was clear. The cardiac impulse was maximal at the lower left sternal border. The second heart sound was unsplit and decreased in intensity at the second left intercostal space. A Grade 3/6, blowing systolic murmur was heard best at the third left intercostal space. No diastolic murmur was heard. The liver was 2 cm below the right costal margin. The remainder of the physical examination was within normal limits

A microhematocrit was 63 per cent. The electrocardiogram showed marked right ventricular hypertrophy with "strain" pattern. The radiologic examination of the chest revealed slightly enlarged cardiac silhouette. The pulmonary artery segment could not be identified, and the pulmonary vasculature was markedly diminished. The clinical diagnosis was pulmonary atresia.

Cardiac catheterization was performed, and 3.5 c.c. of Ditriokon was injected into the left atrium via a foramen ovale. The right ventricle filled partially through a ventricular septal defect, but the



Fig. 1. Film 2: 1/6 second after Film 1. Bronchial arteries on the right are now opacified behind the right atrium.

Autopsy revealed thrombosis of the Teflon prosthesis as the immediate cause of death, undoubtedly aggravated by interference with the extensive collateral circulation in the pleura on the right side. The cardiac anomaly was found to be hypoplastic "left" ventricle, common outflow tract, transposition of the great vessels, pulmonic stenosis, mitral atresia, and a large atrial septal defect. There was no obstruction to flow between the right and left pulmonary arteries, and they were of equal



Fig. 4. Film 2: 1½ seconds after Film 1. Extensive central collaterals on right side.



Fig. 4. Film 4: ½ second after Film 3. Contrast material is sharply increased in the right lung field, associated with gradual disappearance of contrast material in the collaterals.



Fig. 4. Film 3: ½ second after Film 2. Peripheral collaterals are filling. Note particularly the diaphragmatic artery directed toward the right lung field.



Fig. 4. Film 5: 1½ seconds after Film 4. Disappearance of the contrast material from the collaterals The right and left pulmonary [illegible]
now visible [illegible]





Fig. *3* Case 2. *Left:* Before thoracotomy. *Right:* Seven years after thoracotomy, demonstrating marked notching of the ribs on the right side of the chest.

atresia was inferred. With ventricular ejection, a posteriorly located pulmonary artery and an anterior aorta were visualized simultaneously, coming off the single outflow tract. The pulmonic valve was stenotic, and the main pulmonary artery was quite small. Initially, only the left pulmonary artery and left lung field filled with contrast material. The lamination of contrast material in the left pulmonary artery was thought to be suggestive of a central stream of unopacified blood from the right pulmonary artery, flowing in a retrograde direction from the right (Fig. 4) The later films showed good intercostal, internal mammary, and diaphragmatic collaterals which supplied the right lung field. Following this, the pulmonary artery on the right side appeared to be well filled for the first time. This extensive, one-sided collateral circulation was presumably secondary to the thoracotomy on the right side 8 years earlier and confirmed the evidence offered by unilateral notching of the ribs. The higher systemic pressure was ostensibly causing flow in a retrograde fashion through the right pulmonary artery into the left pulmonary artery.

The patient was discharged and later operated upon at another hospital. During right thoracotomy (an unfortunate choice), extremely dense and vascular pleural adhesions were encountered and over 2,000 ml. of blood were lost. An anastomosis was created with Teflon between the subclavian and pulmonary arteries on the right side. Two days after the surgical procedure, the patient died rather suddenly.



Fig. *4*. Case 2. Film 1: With ventricular ejection, the aorta and the left pulmonary artery are visualized. Note the lamination of contrast material in the left pulmonary artery due to central dilution effect, and the absence of contrast material in the right lung field.

and grossly clear lungs. One bronchial artery from the ventral aspect of the aorta at the level of the third intercostal artery supplied the left lung only. An additional very large bronchial artery arose from the right lateral aspect of aorta between the first and second intercostal arteries. This vessel divided, supplying both lungs (Fig. 6). After inflation of the lungs, barium suspension was injected into the descending aorta under pressure; it demonstrated no central connections of the bronchial arteries to the pulmonary arteries. Gross and microscopic evidence of severe, chronic, obliterative pulmonary hypertension were present: dilated pulmonary arteries with macroscopic atheromata, marked medial hypertrophy, and obliterative intimal hyperplasia.

Discussion

The first patient had survived until 3 months of age, and the entire pulmonary flow was through central collaterals predominantly from the bronchial arteries. The degree of opacification of the main branches of the pulmonary artery gives a rough idea of the flow through the collaterals in pulmonary atresia and helps to explain the fact that the pulmonary arteries beyond the atretic point are quite well developed.

The second patient showed considerable gradual improvement after thoracotomy, although no direct surgical anastomoses had been created. The collateral flow, demonstrated with angiocardiography, was through extensive peripheral anastomoses with diaphragmatic and intercostal arteries.

The therapeutic implications of the second case are important. The extent of collateral circulation created by thoracotomy indicates that the subsequent surgical anastomosis should have been performed on the opposite side. Furthermore, the extent of flow through the peripheral

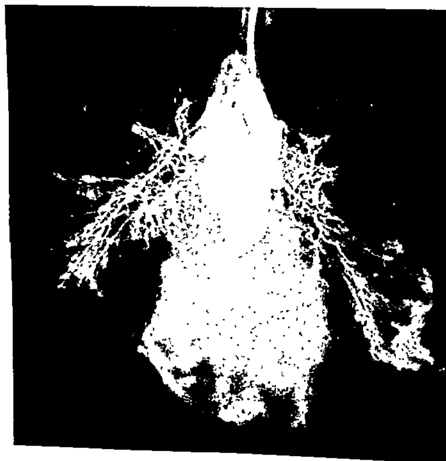


Fig. 6. Case 3. Postmortem injection of the descending aorta, after the intercostal arteries were tied off. The bronchial arteries remain large well out into the parenchyma. The pulmonary arteries are not opacified.

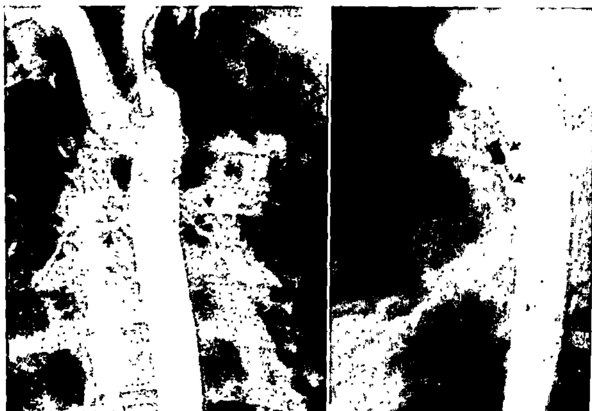


Fig. 5. Case 3. Aortogram, simultaneous frontal and lateral projections, demonstrating enlarged bronchial arteries in a patient with obliterative pulmonary hypertension. There are three branches to the patient's left lung, and one major branch to the right.

caliber. The ductus was not patent. The bronchial arteries were not prominent. There was no evidence of bronchiectasis. The peripheral anastomoses had been largely interrupted by the surgical intervention.

It is evident, therefore, that the failure to fill the right pulmonary artery from the main pulmonary artery meant a higher pressure in the right pulmonary artery, which caused selective filling of only the left by contrast material ejected directly from the ventricle.[17,18] The right pulmonary artery filled subsequently from the collateral circulation.

Case 3 S. L., a 12-year-old girl, was apparently well until 6 months prior to examination, when a murmur was heard upon examination incidental to a bout of bronchitis. Prior to this time, the parents were aware that she became cyanotic upon marked exertion, and that she complained of dyspnea after one flight of stairs.

Physical examination showed early clubbing and duskiness of the lips. There was a loud, unsplit second sound in the pulmonic area, and a soft systolic murmur at the lower left sternal border.

The electrocardiogram revealed right ventricular hypertrophy, with possible combined ventricular hypertrophy. Cardiac series demonstrated a heart which was only moderately enlarged, a very prominent main pulmonary artery, and increased pulmonary vascular markings, which were less prominent in the peripheral lung fields. The hematocrit was 44 per cent.

Cardiac catheterization revealed a modest increase in oxygen content at the right ventricular level, and an additional increase at the pulmonary arterial level. There was a small right-to-left shunt; the sample of blood from the brachial artery was 91 per cent saturated, and increased to 100 per cent with oxygen. The total pulmonary blood flow was 1.6 times the systemic, on room air, and this ratio increased considerably with oxygen. The pulmonary vascular resistance was one half the systemic. The pulmonary wedge pressure was 8 mm. Hg, and the right atrial pressure was 1 mm. Hg. Retrograde aortography was performed to rule out a ductus arteriosus (Fig. 5). This procedure demonstrated the absence of a ductus, and, in addition, it showed the anomalous origin of the brachiocephalic vessels from the aorta, and exceptionally large bronchial arteries. There was no subsequent opacification of the pulmonary artery via the bronchial arteries.

Surgical closure of the ventricular septal defect was performed in spite of the high risk, because of the persistent sizable left-to-right shunt. A large defect, just below the aortic valve, was closed with a Dacron patch. The perfusion and the patient's course during the first 24 hours postoperatively were smooth. However, in spite of grossly clear lungs and absent signs of heart failure, increasing cyanosis developed and the patient died 48 hours after operation. Autopsy revealed water-tight closure of the defect, a small patent foramen ovale,

A new approach to the correction of pure mitral insufficiency by open-heart surgery

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Although open-heart surgery has made remarkable progress in the treatment of congenital heart disease, some major problems in the repair of acquired heart lesions, i.e., mitral insufficiency, remain unsolved. Annuloplasty and plastic additions to the posterior leaflet of the mitral valve have been the most frequently employed techniques.[1,4,7,14,15,17-19,22] It is the purpose of this paper to describe what we believe is a new method for the correction of a type of pure mitral insufficiency.

In pure mitral regurgitation the leaflets are often remarkably pliable; there is no fusion of the commissures, and seldom any calcification.[11,13,14] There is usually some thickening of the leaflets due to scarring and some retraction of the chordae tendineae, plus an actual or apparent loss of substance, predominantly of the posterior leaflet near the posterior commissure. After the initial regurgitation, dilation of the mitral annulus occurs at times as a result of left atrial enlargement and compensatory dilatation and hypertrophy of the left ventricle.

In the surgical research laboratory, using a pulse duplicator, we examined human hearts with pure mitral regurgitation, a small series of hearts with combined stenosis and regurgitation, a series of normal hearts, and a number of canine and calf hearts. A striking finding in the hearts with pure mitral regurgitation was the presence of clefts in the posterior leaflets, which, when closed by sutures, in effect added substance to the posterior leaflets and rendered the valves competent. A high percentage of the normal hearts had these more or less well-developed clefts in the posterior leaflet. Many of the canine hearts and most of the calf hearts had well-developed clefts in the posterior leaflet.

In light of this evidence, we used this technique in operations upon 4 patients with pure mitral regurgitation. None had any stenosis or significant calcification of the leaflets. The annulus was dilated in only 1 patient. All had thickened leaflets, and all had one or two well-defined clefts in the posterior leaflet, through which the predominant initial regurgitation occurred. When these clefts were sutured together, the posterior leaflets were reconstituted and the valves were made competent. The suture technique was identical to that of

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anastomoses suggests that poudrage of the pleural space, perhaps through a needle rather than thoracotomy, should be considered in those patients with markedly diminished pulmonary blood flow and complicated intracardiac deformities for whom no curative operation is possible, particularly when the pulmonary arteries are hypoplastic, which condition precludes major surgical anastomosis.

In the third patient the enlarged bronchial arteries did not connect centrally to the pulmonary arteries. Nevertheless, the mechanism of enlargement was probably that of collateral circulation to peripheral lung deprived of pulmonary arterial flow by the obliterative process of pulmonary hypertension.[21] Demonstration of markedly enlarged bronchial arteries in patients with high pulmonary vascular resistance may be an important clue that the pulmonary vascular disease has advanced to widespread occlusion of pulmonary arteries due to intimal hyperplasia, fibrosis, and thrombosis, and may prove to be a strong contraindication to surgical intervention.

Summary

Two cases of cyanotic congenital heart disease with extensive central and peripheral collateral circulation are presented. Filling of the pulmonary arteries via these collaterals was demonstrated by angiocardiography. A third patient with obliterative pulmonary hypertension had very prominent bronchial arteries but failed to show gross flow from bronchial to pulmonary arteries, either on angiographic or postmortem injection. The enlarged bronchial arteries in this patient probably functioned as collateral circulation to the peripheral lung deprived of pulmonary artery flow by advanced obliterative changes.

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Table I. Cardiac catheterization data in Patient 2

Catheter position	Oxygen content (vol. %)	Pressures (mm. Hg)	
		Phasic	Mean
Right atrium	——	13/7	10
Left atrium	17.18	34/17*	21
Right ventricle	——	64/3	
Main pulmonary artery	9 73	71/29	46
Oxygen capacity	18 69		

Oxygen consumption: 238 c c /min.
Arteriovenous oxygen difference: 7.45 vol. per cent
Cardiac output: 3.2 L./min.
Cardiac index: 2.05 L./min./square meter
Total pulmonary resistance: 1,150 dynes/sec. cm $^{-5}$
Pulmonary vascular resistance: 650 dynes/sec. cm.$^{-5}$

*Left atrial tracing showed a tall v wave with a rapid y descent.

Both clefts were closed with interrupted sutures, reconstituting the arc of the posterior leaflet and rendering the valve completely competent After the termination of bypass, the left atrial pressure was 10/8 mm. Hg. She had an uneventful postoperative course.

On x-ray examination, on Jan 5, 1961, the cardiac size was considerably decreased. There was a high pitched Grade 2 systolic murmur at the apex In June, 1961, she had no dyspnea on exertion and was carrying on her normal household duties The murmur had completely disappeared. She had reverted to normal sinus rhythm, and the electrocardiogram showed marked changes toward normal. Her heart size showed further regression toward normal (see Fig. 2).

Patient 2. Miss A H., an 18-year-old Alaskan girl, had had acute rheumatic fever when she was 11 years old. She had had fatigue and dyspnea on exertion of moderate degree until she was 17, when she was hospitalized for marked congestive failure. She improved with digitalization and diuretics, but was severely incapacitated by fatigue and shortness of breath. Upon examination, she had both right ventricular and left ventricular heaves. There was a Grade 3 to 4 pansystolic murmur and a short rumbling diastolic murmur at the apex. The liver was enlarged to 2 fingerbreadths below the right costal margin.

The electrocardiogram showed atrial fibrillation and left ventricular hypertrophy. Chest roentgenograms showed the heart to be massively enlarged, with a giant left atrium and considerable left ventricular enlargement. There was a moderate degree of pulmonary vascular congestion and small pleural effusions bilaterally. Cardiac catheterization confirmed the clinical diagnosis of predominant or pure mitral insufficiency (see Table I).

She underwent open-heart operation in April, 1961. The mitral valve was grossly incompetent; there was no stenosis. In the posterior mitral leaflet were two clefts which were wide open, and through which the major regurgitation occurred. The slight calcification around the edges of these clefts was thought to be due to turbulence (Fig. 3). The calcium was superficial and could be removed easily from the leaflets. The clefts were closed with interrupted sutures, and competency restored (Fig. 4). There was slight aortic insufficiency, so that intermittent aortic cross-clamping was used to facilitate exposure. After termination of bypass the left atrial pressure was 25/21 mm. Hg, in contrast to 42/25 mm. Hg before bypass. Because of the increased pulmonary vascular resistance demonstrated by cardiac catheterization, and the stiffness of the lungs at the time of operation, a tracheotomy was performed. The postoperative course was smooth, on the second postoperative day the patient converted spontaneously to normal sinus rhythm. She is markedly improved.

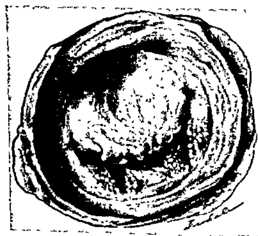


Fig. 3. The mitral valve in Patient 2. Note the slight calcification around the edges of the clefts.

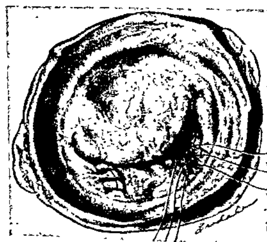


Fig. 4. The mitral valve in Patient 2. The calcium has been removed and the clefts have been closed.

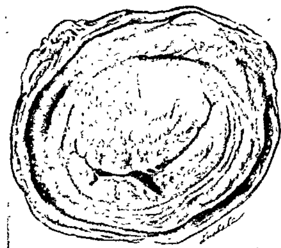


Fig. 1. The mitral valve in Patient 1. Note the clefts in the posterior leaflet through which the major regurgitation occurred. (From Gerbode, et al., Annals of Surgery 155:846, 1962, by permission.)

suturing a congenital cleft in the aortic leaflet of the mitral valve, as is frequently done in endocardial cushion defects.[6] The leaflets in these cases were thickened either from the initial rheumatic carditis or from a combination of this and superimposed turbulence fibrosis; therefore, they held sutures very well. All 4 patients had smooth postoperative courses and are dramatically improved.

Case reports

Patient 1. Mrs. P. S., a 31-year-old woman, was admitted to the Cardiovascular Unit at the Presbyterian Medical Center, in December, 1960. She had had acute rheumatic fever when she was 14 years old, with acute exacerbations when she was 15 and 16. At age 17, she began having dyspnea, palpitations, and pedal edema. She was digitalized after this first of several episodes of congestive heart failure. She was well enough at times, however, to have three full-term pregnancies. During the 6 months before she was hospitalized, fatigue, dyspnea, shortness of breath, and frequent episodes of hemoptysis were progressively incapacitating. On physical examination there was a very prominent left ventricular and right ventricular impulse. The mitral first sound was normal. There was a Grade 5 pansystolic murmur over the apex and left sternal border, and a short diastolic apical rumble. The edge of the liver was palpable, and the liver was tender. There was no pedal edema.

The electrocardiogram showed atrial fibrillation and left ventricular hypertrophy. Chest roentgenograms showed severe cardiomegaly with enlargement of all chambers. A giant left atrium was present.

A clinical diagnosis of rheumatic heart disease with predominant mitral regurgitation was made, and she was operated upon on Dec. 21, 1960. The left atrium was huge and pulsated with each ventricular systole, and had a pressure of 35 mm. Hg.; a large v wave was recorded in the pressure tracing. When the left atrium was opened, two clefts with thickened edges were visible in the posterior leaflet of the mitral valve. The larger of the two was approximately at the mid-point of this leaflet; the other was more anterior (Fig. 1). The regurgitant jet was predominantly through the larger cleft. The annulus was of normal size. There was no calcification of the leaflets and no fusion of the commissures.





Fig. 2. Posteroanterior chest x-ray films of Patient 1. *Top:* Preoperatively. *Bottom:* Six months postoperatively. (From Gerbode, et al., Annals of Surgery 155:846, 1962, by permission.)

Table II. Recordings of pressure (in mm. Hg) at operation

Patient	Bypass status	Left atrial pressure	Systemic pressure
1.	Before	35 (Systolic)	95/60
	After	10/8	100/70
2.	Before	42/25	100/60
	After	25/21	90/60
3.	Before	26/17	140/85
	After	15 (Mean)	110/80
4.	Before	70/20	135/95
	After	18/8	95/60

diastolic rumble at the apex. There was no opening snap. The edge of the liver was not palpable.

The electrocardiogram showed atrial flutter-fibrillation and ST-T abnormalities due to digitalis effect and/or left ventricular hypertrophy. Chest roentgenograms showed a moderately enlarged heart, with considerable prominence of the left atrial contour and both right heart chambers, as well as some enlargement of the left ventricle. The pulmonary vascular tree was slightly engorged.

On clinical grounds, the diagnosis of pure mitral insufficiency was made. At operation, on Aug. 2, 1961, the left atrial pressure before cardiotomy was 70/20 mm. Hg, and the pulmonary arterial pressure was 75/40 mm. Hg. The posterior leaflet of the mitral valve was seen to have a moderately deep cleft near the mid-point of the leaflet, and a small cleft anteriorly (Fig. 5). The regurgitation was predominantly through the large cleft. There was no stenosis and no calcification of the valve. Both clefts were closed with interrupted 4-0 silk sutures. However, since it was noted that the arc of the posterior leaflet was shortened so as to interfere with normal elevation of the aortic leaflet, the two sutures in the small anterior cleft were removed (Fig. 6). After closure of the atrium, the left atrial pressure was 18/8 mm. Hg. The patient made an uneventful recovery, and has shown dramatic clinical improvement.

Table II shows the recordings of pressure obtained at the time of operation, before and after bypass, in the 4 patients reported on.

Discussion

The most common end result of rheumatic mitral valvulitis is a chronic scarring process which leads to mitral stenosis or combined stenosis and regurgitation. Hemodynamically pure mitral regurgitation has been reported, on clinical evidence, to occur in approximately 20 per cent of the patients who develop permanent deformities of the valves after rheumatic fever.[3,22] In papers on the surgery of this condition a similar incidence has been reported. Pure mitral insufficiency may result from ruptured chordae tendineae or from an absolute or relative loss of leaflet tissue. The loss of leaflet tissue has been ascribed to scarring of the leaflets, with contracture, and contraction of the chordae tendineae. The result of such a process would be a deficiency of leaflet tissue as compared to the size of the mitral valve orifice. In addition, this leaflet deficiency is at times increased by a dilatation of the annulus fibrosis. This process undoubtedly accounts for a significant number of cases of pure mitral insufficiency and forms the rationale for annuloplasty, the most commonly applied surgical procedure.

However, there is a significant reserve of leaflet tissue in normal mitral valves, and a dilatation of the annulus is not a constant factor in cases of pure mitral insufficiency. We, as well as others,[7,16] have frequently not noted a dilatation of the annulus when the left atrium was open at the time of operation. The purpose of this communication is to describe another mechanism which results in pure mitral regurgitation. The surgical approach developed from this basis appears to be more satisfactory than that afforded by annuloplasty.

In the early papers on closed mitral surgery, it was frequently stated that exploration of the left atrium revealed that the major initial regurgitant jet occurred through the posterior leaflet near the posterior commissure.[11,21] In addition, the function of the aortic leaflet of the mitral valve was not normal, since it did not balloon out and close the orifice. However, if the exploring finger occluded the posterior jet, the aortic leaflet functioned normally and rose to contact the posterior leaflet.[21] This phenomenon was also demonstrated in our laboratories by the use of a pulse duplicator and supports the well-known fact that insufficiency begets insufficiency.[5] The leaflets must close tightly while the left atrial pressure is low, for, if the left atrial pressure increases beyond a critical level, the function of the aortic leaflet of the mitral valve is impaired.

In *Cunningham's Textbook of Anatomy*[4] it is stated that, "the two cusps [of the mitral valve] are triangular and of unequal size . . . . The bases of the cusps are either



Fig. 5. Photograph of the mitral valve in Patient 4. Note the prominent cleft near the mid-point of the posterior leaflet and the small cleft anteriorly.

Patient 3. Mrs. E. M., a 55-year-old Caucasian woman, had had acute rheumatic fever when she was 7 years old. She had had several bouts of atrial fibrillation and two episodes of suspected pulmonary embolism in 1958. She had been severely incapacitated since November, 1960, after the onset of atrial fibrillation. In May, 1960, she had an episode of acute pulmonary edema. Physical examination disclosed a prominent left ventricular impulse. A late systolic murmur and a short mid-diastolic rumble were heard at the apex. The second heart sound was normally split.

The electrocardiogram showed atrial fibrillation and left ventricular hypertrophy. Chest roentgenograms showed generalized cardiomegaly, with calcification of the mitral annulus. No specific enlargement of the left atrium was noted at the time of this examination. On cardiac catheterization, the left atrial pressure was slightly elevated. There was a prominent *v* wave with rapid *y* descent, consistent with mitral regurgitation. The cardiac output was low. A higher content of blood oxygen was found in the right atrium than in the venae cavae, which suggested the possibility of an additional atrial septal defect or anomalous pulmonary venous drainage.

In June, 1961, she underwent open-heart operation. The right atrium was opened in a search for thrombi, but none were found. The foramen ovale was widely patent, permitting a 14-mm. jet of blood from the left atrium. The foramen ovale was closed with interrupted sutures. After the right atrium was closed, the left atrium was opened. The mitral annulus was enlarged and calcified. In the posterior leaflet were two deep clefts with thickened edges which extended almost to the annulus, and in the aortic leaflet there was a 3-mm. cleft near the posterior commissure. The regurgitant flow was through the two large clefts. There was no stenosis and no valvular calcification. The two large clefts in the posterior leaflet and the small cleft in the anterior leaflet were closed with interrupted 4-0 sutures, reconstituting the arc of the posterior leaflet and rendering the valve completely competent. After the termination of bypass, the mean left atrial pressure was 15 mm. Hg, in contrast to 26/17 mm. Hg before bypass. The patient's postoperative course was uneventful.

COMMENT. At the time of cardiac catheterization and at operation in this patient the left atrial pressure was not so high as it was expected to be on the basis of the patient's history of severe incapacitation with congestive failure and pulmonary edema. This may have been due to the presence of the patent foramen ovale, which undoubtedly increased the pulmonary blood flow, and, although tending to reduce the pressure and size of the left atrium, increased the pulmonary congestion.

Patient 4. Mrs. M. C., a 39-year-old Caucasian woman, had had acute rheumatic fever when she was 8 years old, and had had recurrent attacks of migrating polyarthritis every 3 or 4 years until she was 27 years old. At age 29, after dental extractions, she had had malaise, chills and fever, and a positive blood culture, which was treated successfully with penicillin. She had been on digitalis and diuretics for many years. She had had incapacitating dyspnea on exertion and a chronic cough for as long as she could remember. Examination disclosed a Grade 4 systolic murmur and a Grade 2



Fig. 6. The final appearance of the mitral valve in Patient 4.

particularly significant in the posterior half of this leaflet where there is a small reserve of tissue.

Rheumatic valvulitis causes scarring and contracture of the leaflet tissue and contraction of the chordae tendineae attached to the edges of these clefts, which may cause the clefts to open. It is postulated that these initial areas of regurgitation may increase the left atrial pressure during early systole sufficiently to hinder the normal action of the aortic leaflet of the mitral valve and initiate a vicious cycle, causing significant mitral regurgitation.

In the experimental laboratory and in 4 patients with pure mitral regurgitation, these clefts have been sutured together to reconstitute and shorten the arc of the posterior leaflet and thus restore competency of the mitral valve.

This surgical approach appears to be applicable to a small but significant number of patients with pure mitral insufficiency.

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continuous with each other at their attachments to the fibrous ring around the mitral orifice, or they are separated by small secondary cusps of irregular form and size." Gould's *Pathology of the Heart*[10] states that, "The depth of the notches [in both the mitral and tricuspid valves] is extremely variable, and there may be an increase, or more rarely, a decrease in the number of the leaflets." In 1952, Harken and associates,[12] on the basis of an examination of 35 consecutive normal hearts at autopsy, described four triangular leaflets, arranged circumferentially, as constituting the mitral valve in 75 per cent of these hearts. In other words, the posterior leaflet contained two prominent clefts, which divided this leaflet into an anterior commissural leaflet, a ventricular leaflet, and a posterior commissural leaflet. Rusted, Scheifley and Edwards,[20] in 1952, in a review of 100 normal hearts preserved in formalin, found that 50 per cent of the hearts had significant notching in the posterior leaflet. Fourteen per cent "showed two projections [clefts] in the portions of the posterior cusp adjacent to the commissures. There was one such projection [cleft] in an additional 28 cases. In 13 of these 28 cases, the notching [cleft] existed at the anterolateral portion of the posterior cusp and in the other 15 the posteromedial portion. *In three cases the indentation [cleft] was* at the central portion of the cusp . . . In *each of five cases, four so-called cusps constituted* the posterior leaflet."

If, as reported by Rusted, 29 per cent of normal human hearts have significant clefts in the posterior half of the posterior leaflet of the mitral valve—where, as shown by others, there is little reserve tissue as opposed to the anterior half of this leaflet[2] —then many of these hearts might well have developed predominant mitral regurgitation after rheumatic valvulitis. We postulate that because of slight contraction of the leaflets and contraction of chordae tendineae which are attached around the edges of these clefts, the clefts open and cause the initial regurgitant jet which increases left atrial pressure and interferes with closure of the aortic leaflet of the mitral valve.

That this initial jet may be rather small, 4 to 5 mm. in diameter, and may occur at one or two places, has been seen in 2 of our cases (Patients 3 and 4). In these, inspection of the valve, first, as it functioned with a full left ventricle and, then, after the ventricle had been partially emptied revealed a marked decrease in the jet. Neither patient had any additional valvular abnormality, and when the clefts were closed, the valve was completely competent.

At this time it is not possible to assess the frequency of this mechanism as a cause of rheumatic mitral regurgitation. However, during the past year we have operated upon 17 patients with various deformities of the mitral valve who had significant or predominant mitral regurgitation.[9] Four of these patients form the basis for this report. It would seem, therefore, that this mechanism accounts for a relatively small number of patients with mitral insufficiency and is limited to a percentage of patients with pure mitral insufficiency.

That not all patients with clefts of the posterior leaflet will develop pure mitral insufficiency after rheumatic valvulitis is seen by the fact that in 3 other patients with combined mitral stenosis and regurgitation who were operated upon during the past year, one cleft was present on two occasions, and in one patient two clefts were present. *In such a situation we have* first performed a complete commissur*otomy to mobilize the anterior leaflet,* and have sutured the clefts to shorten the arc of the posterior leaflet. It would appear, however, that in a small but significant number of patients with pure mitral insufficiency who undergo open-heart surgery, clefts in the posterior leaflet are of major importance in causing and perpetuating insufficiency, and that closure of these clefts is a simple and sound technique for restoring competency to the mitral valve in these patients.

Summary

Four patients who had pure mitral insufficiency due to rheumatic heart disease are reported upon; in these patients, satis*factory surgical repair was accomplished by* a simple suture technique.

Clefts are often normally present in the posterior mitral leaflet. These clefts are

absolute change in volume of the finger. The digital volume curve does not necessarily represent the flow of blood through more proximal tissues. In the present communication, it is assumed that the digital volume and the blood flow in the forearm have a rough correlation. The sphygmomanometer cuff was inflated manually, although the inflation bulb is not shown in the illustration. The pressure inside the sphygmomanometer cuff was recorded continuously by the electrical pressure manometer (MP-4T, Nihon Koden, functionally equivalent to the Statham gauge P-23) and was displayed on pen 3 of the recorder. The pressure was also measured subjectively by means of the mercury manometer, and recorded as a dot on the time scale at the top of the illustration.

In the fourth channel, the thoracic movement was recorded as an indication of the respiratory movement. The movement of the thoracic wall was recorded by means of a strain gauge fixed directly on the thoracic wall. In Fig. 2, a small thermistor was placed in the mouthpiece so that the respiration could be registered in terms of the variation in electrical resistance. Here again, the tracing illustrates only the relative movement, and no attempts have been made to measure the absolute change in volume of respiration. The downward deflection indicates the act of inspiration. In Fig. 3, instead of the respiratory tracing, the phasic change in the cuff pressure was amplified and recorded, in the bottom tracing.

More than 40 healthy medical students participated in this experiment. One of

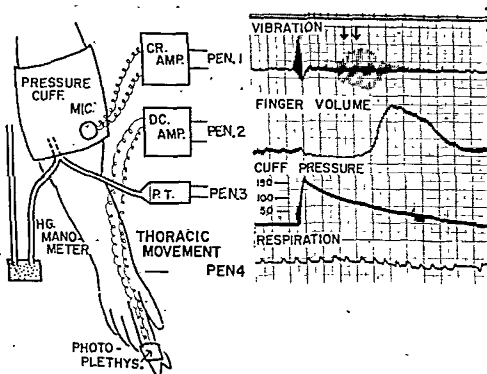


Fig. 1. *Left*: Experimental setup of indirect blood pressure measurement. *MIC.*: Crystal microphone sutured inside the sphygmomanometer cuff. *CR-AMP*: CR-coupled amplifier, time constant 1 second. *P.T.*: Pressure transducer (MP-4T). *Right*: Typical experimental tracings: *Top*, The time interval of 1 second. *Pen 1*, The vibration tracing picked up from the contact microphone; the two arrows indicate where the slight reduction in the amplitude of vibration occurred. *Pen 2*, The finger volume curve; the upward tracing indicates the increase in the blood volume of the finger. *Pen 3*, The pressure inside the sphygmomanometer cuff. *Pen 4*, The respiration curve, the upward deflection indicates the expiration.

Cause of the disappearance of the auscultatory sound in indirect blood pressure measurements

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The presence of an auscultatory gap in the indirect measurement of human blood pressure has been observed frequently among patients, especially those suffering from arterial hypertension. Practically, this source of error can be eliminated by simultaneous palpation of the arterial pulse, which persists throughout an inaudible range of systolic pressure. However, the cause of this auditory gap is still unknown.[7] According to a standard textbook of physiology, the respiratory variation of blood pressure may cause a rhythmic disappearance of the sound, if the systolic level is closely approximated and the decompression is slow.[3] The present experimental design consists of a direct recording of the auscultatory sound, for verification of this rhythmical disappearance of the sound, and for the purpose of obtaining a more precise knowledge of the turbulent flow in systolic pressure.

Methods

Fig. 1 illustrates schematically the method used during this experimental design. A small contact microphone was sutured inside the pressure cuff so that the Korotkoff sounds could be recorded through the convenient low-level RC-coupling amplifier. The time constant of this amplifier was 0.3 second; no special high-cut filter was used for the vibration recording. The vibration tracing was displayed on pen 1 of the four-channel direct-ink-writing recorder. According to Geddes, Spencer and Hoff,[4] the frequencies of the Korotkoff sounds range from 25 to 250 cycles per second. Although the frequency response of the direct-writing pen recorder reduced greatly beyond 70 cycles per second, loss of higher frequency components appeared to be practically negligible.

The continuous recording of the finger volume was displayed on pen 2. The volume recorder consisted of a small pilot lamp and a claire crystal photocell (CL-3). The intensity of the light transmitted through the finger altered the output voltage of the photocell, which was amplified by the direct-coupled amplifier and recorded by the ink-writing recorder. From this tracing, both the peripheral arterial pulsation and the change in volume of the finger can be monitored. No attempts have been made to calibrate the curve in terms of the

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ment in which the grade of respiration was intentionally changed. This was accomplished by having the subject breathe deeply. Fig. 2,*A* shows a tracing similar to that in Fig. 1, but obtained from another subject. The repeated deep respiration, which begins shortly after the beginning of the deflation of the sphygmomanometer cuff, is demonstrated in the bottom tracing. The dot mark superimposed on the time scale coincides with the pressure reading which begins from 170 mm. Hg and ends at 50 mm. Hg. The interval of the two markings indicates a fall of 10 mm. Hg in cuff pressure. It is noted that the definite audible sound is recorded at 140 mm. Hg in this particular instance. Here again, the region of reduction in the vibration tracing can be noticed between 130 and 120 mm. Hg. The reduction in the amplitude of vibration is so remarkable compared to the preceding experiment in Fig. 1, that by auscultation the definite auscultatory gap coincides with the reduced region. It is noted that the reduction in the amplitude of the vibration tracing coincides with the temporal decrease in the upward deflection of finger volume, and also with the onset of inspiration. The decrement in vibration around 100 mm. Hg is also correlated with the onset of deep inspiration, but the large amplitude of vibration indicates that it is an audible sound.

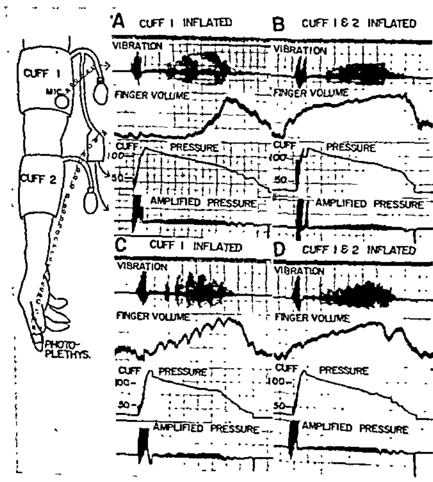


Fig. 3. Effect of the increased peripheral resistance on the Korotkoff sounds. Through an application of the lower pressure cuff (*cuff 2*) the blood flow in the lower arm is occluded in *B* and *D*. Note that the rhythmical variation of Korotkoff sounds decreases in *A*, which suggests that the primary cause of this reduction in amplitude is the change in blood flow.

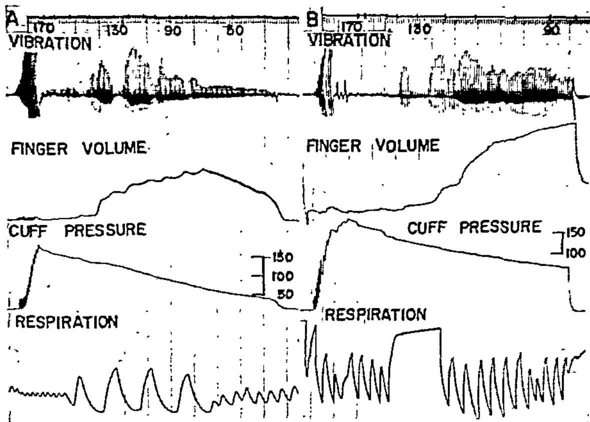


Fig. 2. *A*, Rhythmical variation of vibration tracing due to the deep respiration. *B*, Reduction in the amplitude of vibration due to the temporal arrest of respiration. The amplification of the respiration curve is different in *A* and *B*.

them had a blood pressure reading over 140 mm. Hg; the other readings ranged from 120 to 100 mm. Hg.

Results

A typical vibration recording during measurement of pressure can be seen in the tracings on the right-hand side of Fig. 1. The top markings are the time scale of 1 per second. The vibration tracing is shown in the second row. Since the vibration tracing correlates fairly well with the sound heard by the auscultatory method, we may refer this tracing to the sound tracing. The initial dark triangular deflection indicates the inflation artifact. The duration of this artifact is about 5 seconds, and indicates the time the pressure cuff is inflated. The audible sound begins at about 90 mm. Hg in this particular instance. The amplitude of this sound is about 64 mv., and the deflection gradually increases up through the next four cycles. At the fifth cycle, however, the deflection decreases, as is indicated by the first arrow. In the sixth cycle, the deflection again increases, and at the eleventh cycle the reappearance of the reduction in amplitude is observed. The two arrows on the vibration tracing show where the reduction in the vibration occurred. One can also notice that these points clearly correlate with the onset phase of inspiration. The rapid sweep of the paper indicates the change in wave pattern during this reduction in amplitude. It is suggested, therefore, that these points are related to the clinical manifestation of the pressure measurements. The finger-volume tracing indicates that the flow of blood to the finger does not increase until 70 mm. Hg, where the sound becomes progressively greater.

Since we noticed that a slight decrease in vibration correlated with the respiratory movement, we designed another experi-

bolic. This may explain the cause of the nonlinear increase in finger volume although the pressure falls linearly. The tracing shows that the inaudible zone clearly coincides with the region of high cuff pressure, where the blood flow in the lower part of the cuff appears to be small and below the control level.

The decrease in the flow of blood through the artery tends to decrease the acceleration of the column of blood in the peripheral arterial tree, so that turbulence would temporarily be stopped. On the other hand, the arterial pulse may be palpable, since the cuff pressure is below the systolic pressure. The immediate application of these discussions to auscultatory gaps which are frequently observed in patients must be deferred until more precise observations in patients are available.

Erlanger[3] found that the occlusion of the peripheral artery with the second cuff did not affect the auscultatory sound. The statement is true, as can be seen in tracings *A* and *B* of Fig. 3, and this result indicates that the increase in peripheral arterial resistance does not cause any qualitative change in the auscultatory sound. Under the condition of the combination of deep breathing and application of a tourniquet, the periodic variation in the auscultatory sound disappeared, although the respiratory rhythm remained slightly because of the change in systemic blood pressure. It appears to be reasonable to conclude that the auscultatory gap produced by deep inspiration is due to the decrease in blood flow and not to the rhythmic change in the systemic arterial pressure.

Summary

The correlation between Korotkoff sounds and respiration was studied. The Korotkoff sounds, the finger volume, the sphygmomanometer cuff pressure, and the respiratory movements were recorded on the four-channel direct-writing recorder. The slight reduction in the vibration superimposed on the Korotkoff sounds was reinforced when the subject intentionally continued deep respiration, and the reproducible auscultatory gap was recorded. The cause of this auscultatory gap due to inspiration was suggested to be a decrease in the flow of the blood in the arm.

We are grateful to Professor Sunao Wada for his encouragement throughout the course of this work.

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When the pressure cuff is deflated slowly, the rhythmical variation in the amplitude of the vibration tracing is recorded. In such instances, several inaudible zones have appeared in the vibration record, and it can be demonstrated that the inaudible zone is definitely correlated with the onset of inspiration. Although the reduction in the amplitude of the vibration could be seen in the tracing each time the inspiration began, at the first and second places it was inaudible and at the third gap it was definitely audible, although the sound was muffled. The temporal reduction in the finger-volume tracing also coincides with the inaudible zone.

In Fig. 2,*B* the cuff pressure begins to deflate at about 170 mm. Hg, where the initial dot mark on the time scale is recorded. The following dots on the time scale indicate reductions of 10 mm. Hg of cuff pressure, as is given in the illustration. In this instance, the respiration was intentionally changed by asking the subject to stop his breathing temporarily. Because of this procedure, the blood pressure rose slightly, and during this temporal arrest of the respiration the marked reduction in vibration was recorded. The reduction lasts fairly long and it resembles the clinical auscultatory gap.

Next, the flow of blood in the forearm was intentionally occluded by application of the second pressure tourniquet on the forearm (see Fig. 3), in order to see how the flow of blood in the forearm is related to the inaudible gap. Fig. 3,*A* shows the control tracing before the second tourniquet was applied to the forearm. As was mentioned before, instead of recording the respiratory movement, the small phasic pressure fluctuation in the cuff was amplified, and it is shown in the bottom tracing. Fig. 3,*B* illustrates the results, where the lower cuff is inflated prior to measurement of pressure. No remarkable difference in the vibration tracing is observed between *A* and *B*, except for a slight reduction in amplitude in the vibration. The fact that the systolic blood pressure is slightly elevated appears to be due to spontaneous fluctuation in the blood pressure. The finger-volume tracing is altered remarkably in *B*, which suggests the continuous increment of finger volume through deep arterial supply. Fig. 3,*C* illustrates the effect of deep respiration in the same subject; this tracing was obtained a short while after the previous one, without application of the second tourniquet on the forearm; the remarkable disappearance of the vibration tracing, which coincides with the inaudible zone of the auscultatory method, is noted. It can be seen that the remarkable reduction in finger volume coincides with the inaudible gap, which indicates a decrease in the flow of blood in the finger. Fig. 3,*D* illustrates the effects of the combination of both the deep respiration and the compression of the lower tourniquet. Under this condition, the variation in the sound tracing is remarkably depressed, which indicates that the change in blood flow is the principal factor in the formation of this inaudible gap.

Discussion

Many investigators have made graphic recordings of the Korotkoff sounds.[2,4,6] Geddes, Spencer and Hoff[4] recently recorded the Korotkoff sounds in a normotensive subject, and stated that the auscultatory gap occurs in Phase II, wherein the murmur-like sounds can be heard with the auscultatory method. They did not discuss the mechanism of formation of this gap. The present experiment shows that the auscultatory gap produced by deep inspiration is caused by a decrease in blood flow.

The fact that the volume of the finger did not increase until 90 mm. Hg was reached, and that it then rapidly increased from 90 to 70 mm. Hg, suggests that the flow in an occluded artery follows the formula, *pressure equals flow multiplied by the resistance.* During occlusion of the artery, the resistance may be at its greatest value, and the pressure and the flow both at their minimum. At the time the blood flow resumes in the slightest degree, the pressure in the forearm is lower than that in the upper arm because the resistance to the artery is still considerable. The flow begins to increase slightly, and the resistance decreases slightly, in the next moment. As a result, the pressure under the cuff increases slightly. Therefore, the relationship between the flow and the pressure should not be linear, but hyper-

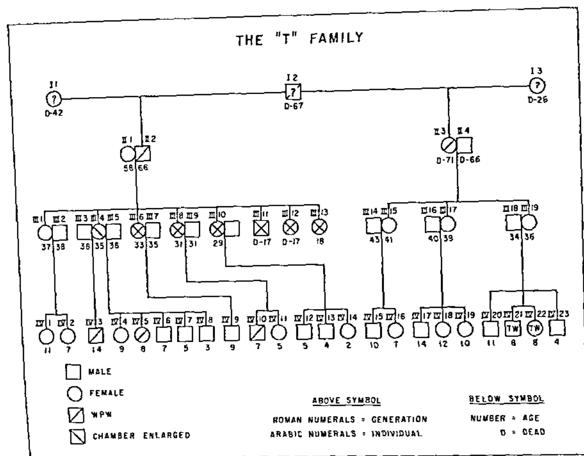


Fig. *1*. Diagram of the T. family tree.

I-2 (1864-1931). He died at the age of 67 years. He was said to have had "heart flutters" during much of his adult life No serious heart difficulty appeared, however, until his mid-sixties. He developed chronic heart failure in his sixty-sixth year; this was associated with some sort of heart block and, finally, uremia. No electrocardiogram or chest x-ray film were taken.

II-2. Born Dec. 12, 1896. Fig. 2. He is presently 66 years old. Heart disease was suspected from a murmur which had been present since childhood Irregularity of the heart was noted when he was 52 years old. Hypertension was noted and treated then An episode of tachycardia and syncope, documented as paroxysmal atrial flutter, occurred when he was 53 years old. Activity was limited by dyspnea and recurrent tachycardia to age 58, when paroxysmal tachycardia was accompanied by frank heart failure He was worse after digitalization to intoxication Digitalis was stopped. Quinidine apparently stopped the arrhythmia. Congestive heart failure has recurred repeatedly until the present time. He has episodes of syncope with tachycardia. He has been in chronic flutter since early 1959. Present medication includes chlorothiazide, rauwolfia, quinidine, and digitoxin. Current symptoms are three-pillow orthopnea, chest pain on lying down only, occasional palpitation, but no swelling of the abdomen or ankles. He is 65 inches tall, weighs 140 pounds, and has a blood pressure of 180/110 mm. Hg. He is orthopneic, with full neck veins The lungs are clear. The heart border is percussed 1 cm outside the midclavicular line in the fifth intercostal space. A Grade 3 aortic systolic murmur is heard transmitted to the neck. There is a decreased aortic second sound, with a short decrescendo diastolic murmur at the base. He has a Grade 2 apical systolic murmur transmitted to the left axilla. Peripheral pulses are intact. He has no hepatomegaly or ascites, and no peripheral edema. Cardiograms show borderline Wolff-Parkinson-White syndrome, and, lately, chronic atrial flutter with controlled ventricular rate.

II-3 (1889-1960). Fig. 3. This woman, a half sister of II-2, had recurrent attacks of palpitation, which were shown to be paroxysmal atrial fibrillation, during the last 20 years of her life. Angina pectoris, with the paroxysmal atrial fibrillation, appeared in her late sixties. Congestive heart failure first appeared 2 months before her death. She had a good response to initial treatment. Acute myocardial infarction occurred on Nov. 1, 1960, with death in shock within 4 hours. Autopsy showed a heart which weighed 350 grams. There was coronary sclerosis, with old and recent occlusions. A fresh occlusion of the left coronary artery above the bifurcation was found. No obvious hypoplasia of the aorta, aortic

Wolff-Parkinson-White syndrome and familial cardiomegaly

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Familial incidence of the Wolff-Parkinson-White (WPW) syndrome has been pointed out by many observers, including Öhnell,[1] McIntire,[2] Averill,[3] Sökmen,[4] and Harnischfeger.[5] The family which herein is reported upon represents a clear example of familial and congenital WPW syndrome, and illustrates the diversity of expression of the trait, its generally dominant inheritance, and its occasionally lethal character. This family also represents the concurrence of familial cardiomegaly, presenting the clinical picture described by Evans,[6] Campbell,[7] Gaunt,[8] and Schiebler.[9]

Rodbard[10] and, later, Brock[11,12] pointed out the occurrence of functional obstruction of the outflow tracts of the right and left ventricles. Braunwald[13] pointed out the possible association of WPW syndrome with "functional subaortic stenosis," and the resulting left ventricular hypertrophy, especially when the anatomic change presents itself for the first time in the second and third decades of life.

The clinical features of familial cardiomegaly were described by Evans,[6] who named the syndrome. There are no symptoms during the first decade of life, and physical and laboratory examination during that time may reveal no abnormalities. During the second and third decades, arrhythmias, syncopal attacks, cardiomegaly, and, occasionally, sudden death occur. A characteristic cardiac silhouette in the chest x-ray film was described by Kremer.[14] Atypical systolic murmurs along the left sternal border are common, and were first described by Evans.[6] According to Braunwald,[13] angiocardiography reveals encroachment upon the outflow tract of the left ventricle, from both the septum and the free wall, and distortion of the mitral valve. At operation or autopsy, this is found to be muscular hypertrophy. Gaunt[8] described the microscopic findings to be hypertrophied muscle fibers with vacuolization and increased glycogen content, without increased glycogen in other organs, such as the liver. The coronary arteries are said to be small.

Case study

Fig. 1 diagrams a family tree, showing the occurrence of cardiac abnormalities. All living members had posteroanterior chest films, 12-lead electrocardiograms, and were examined by the senior author. A summary of clinical data concerning those members with significant cardiac abnormalities found by physical examination, chest x-ray film, and ECG follows.

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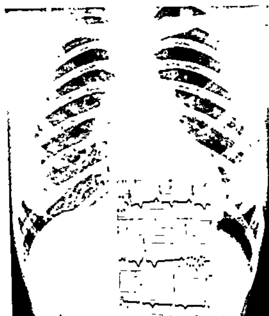


Fig. 5. III-6. Chest x-ray film of Dec. 29, 1958, showing prominence of the left border above the apex. ECG of Dec. 29, 1958, showing pre-excitation Leads I, II, III.

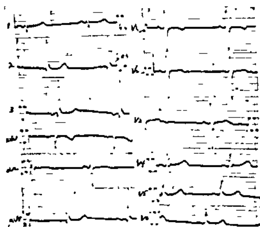


Fig. 6. III-8. ECG of Aug. 16, 1959, double-speed, showing borderline pre-excitation. Leads I, II, III

Wolff-Parkinson-White syndrome was demonstrated by electrocardiogram in 1952. Borderline enlargement of the heart was noted on x-ray examination in 1956. Parasternal and apical systolic murmurs were heard after 1956. She has had three normal pregnancies and deliveries—1956, 1958, and 1959. She is currently gravida IV. Episodes of palpitation occurred during the second trimester of pregnancy in 1959 Longer runs of tachycardia occurred in August, 1959; she was treated with quinidine after delivery of her third child. She was catheterized in 1960; no defect was demonstrated. She currently shows cardiomegaly which involves the left ventricle, and Wolff-Parkinson-White syndrome with false left bundle branch block. Paroxysmal tachycardia is not yet documented by electrocardiogram.

III-12 (1935-1953). Fig. 8. He died at the age of 17 years. A systolic murmur was heard parasternally and apically when he was 16 years old. Borderline enlargement of the heart was noted then, on physical examination. An electrocardiogram on March 23, 1951, when he was 16 years old showed nodal rhythm with Wolff-Parkinson-White syndrome. In 1953, he died suddenly after moderate exertion while playing

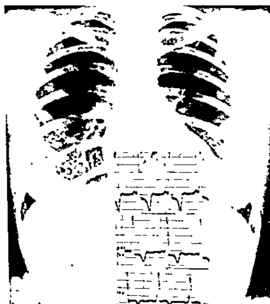


Fig. 7. III-10. Chest x-ray film of Sept 13, 1959, showing prominence of the left border above the apex. ECG of June 13, 1959, showing pre-excitation. Leads I, II, III.

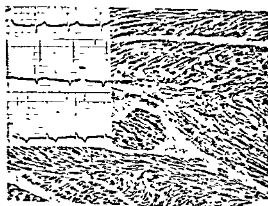


Fig. 8. III-12. Microscopic section of heart, showing hypertrophy and fibrosis. ECG of March 23, 1951, showing pre-excitation. Leads I, II, III.

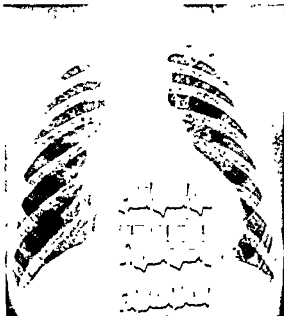


Fig. 2. II-2. Chest x-ray film of March 23, 1959, showing generalized enlargement. ECG of April 1, 1954, showing pre-excitation. Leads I, II, III.

rings, or coronary orifices was noted. There was moderate left ventricular enlargement; the wall of the left ventricle measured 2 cm. in thickness. No valvular or septal defects were found. Electrocardiograms have shown pre-excitation with false bundle branch block.

III-4. Born July 24, 1927. Fig. 4. This woman has no cardiac symptoms at present. The blood pressure has always been normal. She has had six pregnancies and deliveries, without difficulty. Cardiomegaly was found by x-ray examination when she was 25 years old, but not since. She has an abnormal electrocardiogram, which shows a normal P-R interval but abnormal intraventricular conduction, with voltages which suggest left ventricular enlargement. Examination reveals a parasternal systolic murmur, Grade 2 in intensity, with normal first and second heart sounds at the apex and base. Currently, she shows no clinical enlargement, by physical or x-ray examination.

III-6. Born Sept. 16, 1929. Fig. 5. Palpitation and heart consciousness appeared when she was 24 years old, after the death of her brother (III-11). A slightly enlarged heart and Wolff-Parkinson-White syndrome were noted then. Paroxysmal tachycardia has occurred since 1957. Cardiac catheterization was carried out in 1957, and no abnormality was demonstrated. Presently, she is heart conscious, without real evidence of disease, except borderline cardiac enlargement, and Wolff-Parkinson-White syndrome in her electrocardiogram. She has been treated symptomatically with sedatives and has shown improvement.

III-8. Born April 26, 1931. Fig. 6. This woman has no cardiac symptoms or signs. A borderline ventricular enlargement was shown on the x-ray film, but not by physical examination. Type-A Wolff-Parkinson-White syndrome is suggested, but not clear cut, in her double-speed electrocardiogram. Both P-R and QRS are 0.10 second. There is nodal rhythm. The electrocardiogram shows a prominent R wave in Lead V_1, and a vertical position.

III-10. Born Feb. 15, 1933. Fig. 7. This woman showed no cardiac symptoms or signs until 1960.

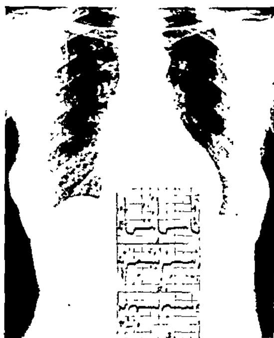


Fig. 3. II-3. Chest x-ray film of June 2, 1950, showing generalized cardiac enlargement. ECG of May 27, 1958, showing pre-excitation. Leads I, II, III.

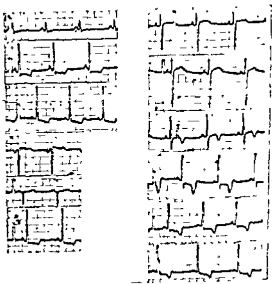


Fig. 4. III-4. ECG of Jan. 19, 1960, showing borderline pre-excitation. Leads I, II, III.

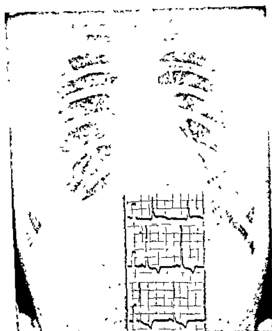


Fig. 11. III-14. Chest x-ray film of Dec. 27, 1960 showing only slight prominence of the left border above the apex. ECG of March 23, 1959, showing pre-excitation. Leads I, II, III

(short P-R interval with normal QRS duration). Two of the 8 children of II-2 have died suddenly, ironically at the same age, 17, and on the same playground.

The second oldest of these siblings, III-4, has borderline changes in her electrocardiogram (Fig. 4). She has produced 2 children (by different fathers), IV-3 and IV-5, both of whom show similar borderline electrocardiograms. Both fathers are normal.

The other third-generation member with borderline Wolff-Parkinson-White syndrome, III-8, has produced a child (IV-10) who shows a borderline WPW electrocardiogram.

None of the other fourth-generation members show electrocardiographic or cardiac abnormality, to date. But neither did III-14 until her second decade. III-8 and III-4 had normal electrocardiograms until their third decade.

Of interest is the change in electrocardiograms toward the classic WPW syndrome seen in III-14 (Figs. 10 and 11). She is now 18, barely past the age of death of two siblings. Her cardiac silhouette, although typical, fails to show the marked abnormality of the left ventricular border seen in the x-ray film of her dead sister, III-13 (Fig. 9).

The similarity of cardiac silhouette, especially along the left border from above the apex to the pulmonary conus, is seen in Figs. 2, 3, 5, 7, 9, 10, and 11. This may represent hypertrophy of the outflow tract in individuals with WPW syndrome.

The data presented suggest that Type-B Wolff-Parkinson-White syndrome indeed may produce "functional subaortic stenosis," leading to hypertrophy of the outflow tract of the left ventricle. Generalized hypertrophy of the left ventricle then follows. The finding of hypertrophy of the outflow tract of the right ventricle in persons with Type-A WPW syndrome (initial upward deflection in right precordial leads) would support the existence of such a mechanism if it can be demonstrated. Although the electrocardiogram of III-8 suggests right ventricular predominance, her cardiac silhouette is not yet typical of lesser chamber enlargement.

The variation in pace of enlargement through life, as illustrated by this family, would seem to depend on how much pre-excitation took place, its direction in the ventricle, and what percentage of the time pre-excitation replaced normal conduction.

Sudden death apparently results from arrhythmia, tachycardia, or ventricular fibrillation, compounded by inadequate coronary circulation.

Possible prevention of sudden death by drugs—atropine to favor atrioventricular nodal conduction, or quinidine to prevent tachycardia—may be possible when WPW syndrome and cardiomegaly coexist. Closed-heart massage has been taught this family. Open-heart operation to relieve obstruction of the outflow tract, as reported by Braunwald,[13] may be useful in selected cases.

Summary

A family in which several members have evidence of WPW syndrome, and of familial cardiomegaly, with several instances of sudden death, has been described. The possible connection between the physiologic anomaly, i.e., pre-excitation, and the anatomic changes has been discussed.

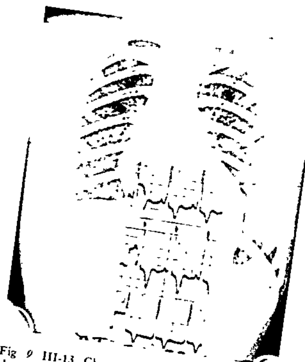


Fig 9 III-13 Chest x-ray film of July 10, 1952, showing prominence of the left border above the apex. ECG of March 23, 1952, showing pre-excitation Leads I, II, III.

baseball Autopsy showed a heart which weighed 500 grams The left ventricular wall measured 2.0 cm., and the right ventricular wall measured 0 7 cm The circumference of the aortic valve was 5 6 cm, and the diameter, 1 6 cm. The coronary artery orifices were said to be small. The muscle of the left ventricle was pale, grossly Microscopic examination showed hypertrophied fibers with disarrangement of muscle bundles and scattered fibrosis.

III-13 (1937-1954) Fig 9. This girl died when she was 17 years old She was asymptomatic. An enlarged heart had been noted on physical examination when she was 15 years old The blood pressure was as high as 150/100 mm Hg on one occasion. Other blood pressures were normal Left ventricular enlargement was suggested by chest x-ray examination The Wolff-Parkinson-White syndrome was noted in the electrocardiogram. She died suddenly after moderate exertion during a gym period. No autopsy was performed

III-14 Born Jan 29, 1944 Figs. 10 and 11. She has no symptoms. No cardiomegaly is apparent on physical examination. X-ray silhouettes since 1960 suggest left ventricular hypertrophy. There is a systolic murmur, Grade 1, at the apex She had normal electrocardiograms until she was 13 years old, when Wolff-Parkinson-White syndrome was found. There are no heart symptoms at present.

IV-3. Born 1948 This boy has no cardiac symptoms or signs. There is normal heart size on physical and x-ray examination. The electrocardiogram shows a borderline Wolff-Parkinson-White syndrome, with abnormal T waves in precordial leads V_2 and V_4, and a P-R interval of 0 08 second, but a QRS of only 0 08 second.

IV-5. Born 1953. There are no cardiac symptoms or signs. Physical and chest x-ray examination show her to have a normal-sized heart. Electrocardiograms, however, show borderline Wolff-Parkinson-White syndrome, identical to that found in the tracings of her half brother, without the T-wave abnormalities.

IV-10 Born 1955. This boy has no cardiac symptoms or signs A normal-sized heart was noted by physical examination. An electrocardiogram shows borderline Wolff-Parkinson-White syndrome, with P-R of 0 09 second and QRS of 0.09 second.

Comment

The common parent of II-2 and II-3 was I-2, who had "heart flutters," but no electrocardiogram was taken. He may have had WPW syndrome. II-2, and his half sister II-3 show pre-excitation, but minimal difficulty until their sixties. None of the descendants of II-3, all of whom were studied, show abnormalities.

Seven out of 8 of the children of II-2 have abnormalities; his wife's heart is normal. Five of these third-generation siblings have clear-cut Type-B Wolff-Parkinson-White syndrome (predominant downward deflection in Lead V_1); the other 2 show borderline abnormalities

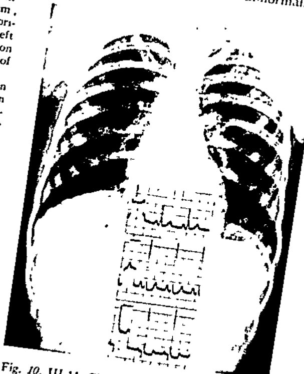


Fig. 10. III-14. Chest x-ray film of July 10, 1952, showing slight prominence of the left border above the apex. ECG of July 11, 1952, showing normal conduction. Leads I, II, III.

Adrenocortical function in hypertensive and nonhypertensive patients

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The factor of excessive adrenal cortical activity has been considered previously in clinical hypertensive disease. However, precise correlations have not been previously reported. The purpose of this study was to determine the incidence of adrenocortical hyperresponsiveness to corticotrophin among hypertensive subjects and a comparable group of nonhypertensive subjects.

Materials and methods

The subjects of this study were 50 patients who were attending the hypertensive outpatient clinic, and 50 nonhypertensive patients from the medical service wards of the Veterans Administration Hospital, Houston, Texas. Control 24-hour urinary excretions of 17-ketosteroids and 17-ketogenic steroids were determined, using the Norymberski technique.[1] These studies were repeated after stimulation with corticotrophin. The corticotrophin stimulation test was performed as follows: A 24-hour (control) specimen of urine was collected on the first day. The following day at 4 P.M., 80 units of corticotrophin (Organon) was given intramuscularly. Sixteen hours later, at 8 A.M. on the third day, another 80 units of corticotrophin was given, and collection of a 24-hour specimen of urine (drug) was started immediately. This study was done using the double-blind technique; that is to say, the technician doing the analyses and the investigator analyzing the data did not know whether the patient was hypertensive or in the control group.

Results

Hypertensive group (*Table I*). The average control urinary excretion of 17-ketosteroids in this group of patients was 15 mg. per 24 hours (range: 6 to 39 mg. per 24 hours), whereas the average excretion of 17-ketogenic steroids was 24 mg. per 24 hours (range: 5 to 67 mg. per 24 hours). After corticotrophin stimulation the average urinary excretion of 17-ketosteroids was 32 mg per 24 hours (range: 12 to 73 mg. per 24 hours), and the average excretion of 17-ketogenic steroids was 66 mg. per 24 hours (range: 16 to 182 mg. per 24 hours). Of these 50 patients, 38 were receiving diuretics as part of their antihypertensive therapy. The average values for these 38 patients were as follows: the control excretion of 17-ketosteroids was 15 mg. per 24 hours, and of 17-ketogenic steroids, 23 mg. per 24 hours. After corticotrophin stimulation the average urinary excretion of 17-ketosteroids was 30 mg. per 24 hours, and of 17-ketogenic steroids, 63 mg. per 24 hours, which indicates no significant difference when compared to the total group.

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The status of the myocardial arterioles in angina pectoris

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The symptom complex of angina pectoris is nowadays public knowledge and a medical commonplace. It is surprising that the first clear reference to the disease in the literature appeared as late as the seventeenth century.[1] In the latter half of the eighteenth century, William Heberden[2] wrote a classic description of the symptomatology of angina of effort and placed it among the spasmodic complaints. Some years later, Parry[3] uncovered the association of angina with ischemia of heart muscle.

Authorities now agree that the anginal syndrome is due to myocardial anoxemia.[4,5] Osler[6] described a number of diseases associated with anginal pain, but degenerative coronary artery disease is by far the most common etiological agent. Lenègre and Himbert[7] found significant coronary atherosclerosis in 80 per cent of necropsy hearts in an unselected anginal group; and when angina had been the only clinical abnormality, significant atherosclerosis was present in 100 per cent of the cases.

The important investigations of Blumgart, Schlesinger and Davis,[8] and Zoll, Wessler and Blumgart[9] involved injecting the coronary system with a radiopaque mass but did not include a systematic study of the walls of the small arteries and arterioles. The conclusion was that the theory that arterial spasm produced relative myocardial ischemia was unproved, but that spasm and vasomotor effects which reduce coronary flow are in no way incompatible with the widespread pathologic effects demonstrated.

There is a paucity of descriptive or quantitative morphologic studies of the small intramural coronary arteries in patients with anginal heart disease. For years, one of us (S. C. Sommers) had noted that the myocardial arteriolar walls were thicker than usual in patients with angina. The senior author was uncertain whether this relationship existed. Consequently, these vessels have now been measured in order to determine whether they exhibited a muscular hypertrophy that would be consistent with a spastic tendency in life, and whether they demonstrated any unusual thickening or significant luminal narrowing that would contribute to the adverse effects of obliterative and sclerotic disease of the larger vessels. The statistical analyses subsequently performed were *not* utilized to establish that differences existed, but to estimate the degree of the arteriolar alterations in angina that had become evident from the histopathologic study.

Materials and methods

Histologic sections were made from 50 necropsy hearts. The anginal group consisted of 20 hearts taken from subjects with

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Table I. Effect of corticotrophin stimulation on the urinary adrenocortical excretion in hypertensive and nonhypertensive patients (average values for 50 subjects in each group)

Group	Control excretion (mg./24 hr.)		Drug excretion* (mg./24 hr.)	
	17-Ketosteroids	17-Ketogenic steroids	17-Ketosteroids	17-Ketogenic steroids
Hypertensive	15	24	32	66
Range	6-39	5-67	12-73	16-182
Nonhypertensive	17	30	31	72
Range	8-28	13-58	15-61	24-196

*Urinary excretion values after stimulation with corticotrophin

Nonhypertensive group (*Table I*). The average control urinary excretion of 17-ketosteroids in this group was 17 mg. per 24 hours (range: 8 to 28 mg. per 24 hours), whereas the average excretion of 17-ketogenic steroids was 30 mg. per 24 hours (range: 13 to 58 mg. per 24 hours). After corticotrophin stimulation the average urinary excretion of 17-ketosteroids was 31 mg. per 24 hours (range: 15 to 61 mg. per 24 hours), and the average urinary excretion of 17-ketogenic steroids was 72 mg. per 24 hours (range: 24 to 196 mg. per 24 hours).

Summary

The urinary excretion of 17-ketosteroids and 17-ketogenic steroids has been studied in 100 subjects (50 hypertensive and 50 nonhypertensive), using a double-blind technique. The data of this study indicate that there is no significant difference in the urinary excretion of 17-ketosteroids and 17-ketogenic steroids by nonhypertensive and hypertensive patients. As has been noted previously,[2] there was also no significant difference in the influence of diuretics upon the excretion of steroids.

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sections were examined from both Zenker and formalin-fixed material. Some sections were those made by the original prosectors. Usually, additional sections were cut from preserved stock tissue. A majority of the sections were stained by the Masson trichrome method. A minority were stained with routine hematoxylin and eosin. The Masson trichrome stain facilitated the identification of the muscle components of the vessel walls. The specimens were derived from many different parts of the myocardium.

Variations in the histopathologic material ascribable to postmortem intervals, duration and type of fixation, and methods of tissue processing and staining influenced the appearance of the myocardium, but the walls of the myocardial arterioles were not appreciably affected. The sections were regularly cut perpendicular to the epicardial surface; and in all three groups studied, grossly evident foci of atrophy, fibrosis, degeneration, or hypertrophy of the myocardial fibers were occasionally included. The technique used by the prosectors provided, practically exclusively, pieces of left ventricular and interventricular septal myocardium not otherwise selected grossly or microscopically.

Measurements were made using an optical micrometer with medium magnification (×320). Twenty vessels were measured from each heart. They were located largely in the substance of the myocardium in interstitial planes. An attempt was made to include only vessels that had apparently been cut substantially perpendicular to their course, but many vessels were not wholly circular in outline, so that some estimations of total diameters were necessary. Limitations of material, time, and money were responsible for the decision to measure only 20 arterioles per heart.

The vessels measured were selected somewhat arbitrarily as to size, since no agreement on the limits of arteriolar size was found among authorities consulted.[10-13] We have concluded that the word *arteriole* is a semantic conundrum when used in a morphologic sense. The smallest arteriolar vessels included in the study were the largest ones that consistently showed only a single muscle layer in their walls. The largest included were vessels that most authors would designate as "arteries." They represented the largest vessels seen with any frequency in the myocardial interstitium. The range of total outside arteriolar diameters measured thus was from 40 to 280 μ. We agree with Saphir and associates[14] that the adventitia merges imperceptibly into the adjacent interstitial tissue; hence, only the intima and media were included in the measurements.

When more than 20 vessels suitable for measurement were seen in sections cut from a single heart, all of the larger vessels available for study were included rather than only those of minimal diameter. This was done because the smallest vessels inevitably comprised much the largest group numerically, and thus imparted a bias to the total average results which was thought to be undesirable, even if

Table II. Distribution of diameters of vessels measured

Diameters (micra)	Number			Percentages		
	Anginal	Control	Normal	Anginal	Control	Normal
40–76	200	241	124	50	60.25	62
80–116	120	101	56	30	25.25	28
120–156	45	30	12	11.25	7.5	6
160–195	15	14	4	3 75	3.5	2
200–236	8	6	4	2	1.5	2
240–276	6	3	0	1.5	0.75	0
280	6	5	0	1 5	1 25	0
Total	400	400	200	100	100	100

Table I. Age, sex, duration of angina and diseases in control cases

Anginal				*Control*				*Normal*			
Age (yr.)	*Sex*	*Heart weight (Gm.)*	*Duration (yr.)*	*Age (yr.)*	*Sex*	*Heart weight (Gm.)*	*Disease*	*Age (yr.)*	*Sex*	*Heart weight (Gm.)*	*Disease*
43	M	340	1	44	M	410	Lymphoma	23	F	180	Injury
47	M	700	6	44	M	380	Mesenteric infarct	24	M	320	Thymic carcinoma
51	M	400	"Recent"	52	M	230	Lymphoma	25	M	320	Injury
54	M	460	4	55	M	340	Carcinoma of colon	25	M	450	Injury
54	M	—	Long standing	57	M	440	Cirrhosis	28	M	280	Brain tumor
58	M	450	"Some"	58	M	490	Mediastinal goiter	31	F	305	Polio
63	M	370	1½	59	M	310	Carcinoma of lung	34	M	400	Polio
66	M	450	2	64	M	170	Carcinoma of esophagus	35	F	350	Polio
67	M	610	10	67	M	190	Lymphoma	35	F	270	Polio
67	M	570	5	67	M	290	Carcinoma of stomach	38	M	360	Polio
69	F	450	15	68	M	500	Carcinoma of lung				
70	F	380	8	71	F	290	Transverse myelitis				
70	M	600	"Unknown"	71	M	380	Carcinoma of lung				
72	M	570	10	72	M	370	Reticulum cell sarcoma				
73	M	870	17	72	M	510	Septicemia				
74	M	440	2	73	M	280	Carcinoma of stomach				
75	M	550	7	74	M	—	Carcinoma of appendix				
77	F	600	5	75	F	410	Carcinoma of breast				
78	F	420	12	76	F	320	Carcinoma of stomach				
78	F	470	Long standing	76	F	340	Carcinoma of bile duct				
Mean 65		511± 130		65		350± 97		30		324± 74	

a well-established clinical history of angina pectoris (Table I). Cases were rejected as unsuitable for inclusion when the autopsy findings cast doubt on the validity of the clinical diagnosis. No cases of chest pain after proved myocardial infarction or associated with other types of thoracic disease that may simulate angina pectoris were included.[4-6] The final pathologic diagnosis determined whether a case would be studied further. The anginal cases were matched by age and sex with a control group in which there was no previous history of angina, and any other disease state or symptomatology was allowed. Inevitably, cases of more or less severe arteriosclerotic heart disease were included. A third group comprised 10 hearts designated as "normal," which were taken from young subjects without historical or autopsy evidence of coronary disease, and without the finding of vascular disease other than, at most, minimal aortic atheromatous streaks.

The risk of bias in the material thus collected would be increased by different admission and autopsy rates for the three groups, which could perhaps spuriously relate arteriolar changes to one group or another. So far as can be determined, admission rates were highest for the control group, intermediate for the anginal group, and lowest for the normal group. Autopsy rates for each were approximately equivalent, and this allowed a wider choice of control cases matched as to sex and age. To the limited extent that multiple possible known and unknown factors of bias could be appraised, the material was considered to be relatively weighted toward finding more arteriolar disease in the control group than in the anginal group, and the least amount in the normal group.

Routine, paraffin-embedded, histologic

Table V. Analysis of variance and means by groups

		Anginal	*Control*	*Normal*
Diameter	Variance	140 69	120 25	72 14
	Coefficient of variance	54 79	55 82	46 10
	Mean (μ/4)	21.65± .59	19 63± 55	18 42± 60
Thickness	Variance	6 62	4 35	1 64
	Coefficient of variance	62.63	58 25	34 51
	Mean (μ/4)	4 11± .13	3 58± 10	3 71± .09
Muscle layers	Variance	2 593	1.330	0 928
	Coefficient of variance	63 72	57 35	42 32
	Mean	2.527± 083	2 011± 06	2 276± 068

Table VI. Statistical comparisons of groups

	Diameter		*Thickness*		*Muscle layers*	
	Variance	*Mean*	*Variance*	*Mean*	*Variance*	*Mean*
Anginal: Control	Not significant (p > 05)	Significant (p < .05)	Significant (p < 01)	Significant (p < 001)	Significant (p < 01)	Significant (p < .05)
Control: Normal	Significant (p < 01)	Not significant (p > 05)	Significant (p < 01)	Not significant (p > .05)	Significant (p < .01)	Significant (p < 05)
Anginal: Normal	Significant (p < 01)	Significant (p < 001)	Significant (p < .01)	Significant (p < 02)	Significant (p < 01)	Significant (p < .05)

Table VII. Analysis of variance for wall thickness

Variation	*Anginal*			*Control*			*Normal*		
	df	*MS*	*F*	*df*	*MS*	*F*	*df*	*MS*	*F*
Between hearts	19	13 55	2 21	19	8 86	2 14	9	4 19	2 16
Within hearts	380	6 13	p ≐ 005	380	4 13	p ≑ 005	190	1 52	p ≑ 005
Total groups	399	7 62		399	4 35		99	1 64	

Table VIII. Analysis of variance for diameter

Variation	*Anginal*			*Control*			*Normal*		
	df	*MS*	*F*	*df*	*MS*	*F*	*df*	*MS*	*F*
Between hearts	19	217.7	1 59	19	186 5	1 60	9	233 6	3 62
Within hearts	380	137 3	p ≑ 05	380	116 9	p ≑ 05	190	64 5	p < 001
Total	399	140 7		399	120.3				

Table III. *Distribution of thicknesses of vessel walls*

Thickness (micra)	Number			Percentages		
	Anginal	Control	Normal	Anginal	Control	Normal
4	2	0	0	0 5	0 0	0.0
8	92	127	32	23	31 75	16
12	117	122	66	29 25	30 5	33
16	70	72	56	17 5	18 0	28
20	56	39	29	14 0	9 75	14 5
24	21	12	12	5.25	3 0	6 0
28	10	9	4	2 5	2.25	2 0
32	7	9	0	1 75	2 25	0 0
36	5	1	0	1 25	0 25	0 0
40	10	6	1	2 5	1 5	0 5
44	1	0	0	0 25	0 0	0.0
48	4	1	0	1 0	0 25	0 0
52	0	0	0	0 0	0 0	0 0
56	0	0	0	0 0	0 0	0.0
60	2	1	0	0 5	0 25	0 0
80	3	0	0	0 75	0 0	0 0
100	0	1	0	0 0	0 25	0 0
Total	400	400	200	100	100	100

Table IV. *Number of muscle layers in vessel walls for each group*

Layers (number)	1	2	3	4	5	6	7	8	14	None	Total
Number anginal	90	146	72	33	12	7	5	8	1	26	400
Number control	127	136	60	17	15	2	1	0	0	42	400
Number normal	38	94	46	18	2	0	1	0	0	1	200
Per cent anginal	22 5	36 5	18	8 25	3	1 75	1 25	2	0 25	6 5	100
Per cent control	31 75	34	15	4.25	3 75	0 5	0 25	0	0	10 5	100
Per cent normal	19	47	23	9	1	0	0 5	0	0	0 5	100

partially inescapable. Estimated diameters were established partly by determining the mean of the longest and shortest external diameters,[15] but, since perfect ovality was seldom observed, some reliance was placed on the synthetic ability of the "trained eye." The thickness of the wall was taken as that observed most generally around the circumference, i.e., the average thickness. No attempt was made to establish a mean thickness, but a note was made of the maximum thickness when this differed from the average value. Finally, in the majority of vessels, the numbers of layers of circular muscle cells in the media were counted. In some vessels the muscle layers were partially replaced by connective tissue, so that, consequently, the counting of layers was impossible. This difficulty was encountered with approximately equal frequency in the anginal and control groups. Hypertension with arteriolar nephrosclerosis was present in 14 anginal and 11 control cases, but in no normal cases. The heart weights are given in Table I. In a few of the sections examined early in the study, counts of muscle layers were not attempted in all the vessels examined. Thus, the total number of vessels wherein the count of muscle layers was not recorded is 69, and the number wherein counts were made is 931.

The accumulated data were used to construct frequency distributions for diameters, thicknesses, and numbers of muscle layers for each vessel and group.

Table IX. Frequency distribution and means of vessel diameters and thicknesses for different numbers of muscle layers

Layers	*Anginal*			*Control*			*Normal*		
	Number	*Mean diameter*	*Mean thickness*	*Number*	*Mean diameter*	*Mean thickness*	*Number*	*Mean diameter*	*Mean thickness*
1	90	52 88	8 64	127	50 68	8.76	38	47 15	9 68
2	146	70 88	12 92	136	69 92	12 56	94	62 60	13 20
3	72	98 16	17 84	60	91 00	17 32	46	89 92	18 08
4	33	131 88	23.88	17	153 40	22 12	18	124 68	22 44
5	12	146 68	29 32	15	177 32	30 92	2	220 00	28 00
6	7	150.84	35 44	2	220.00	30 00	0		
7	5	176 00	43 20	1	180 00	40 00	1	180 00	40 00
8	8	231 00	54 48	0			0		
14	1	280.00	80.00	0			0		
Not counted	26	87 68	19 52	42	97.12	22.20	1	60 00	20 00

Table X. Frequency distribution and means of vessel diameters and muscle layers for different thicknesses

Thickness	*Anginal*				*Control*				*Normal*			
	Number	*Mean diameter*	*Number*	*Mean layers*	*Number*	*Mean diameter*	*Number*	*Mean layers*	*Number*	*Mean diameter*	*Number*	*Mean layers*
4	2	44 0	2	1 0	—	—	—	—	—	—	—	—
8	92	52 92	91	1.23	127	50 52	122	1 14	32	44 88	32	1 25
12	17	68 40	109	1 98	122	66 12	114	1 86	66	57 20	66	1 86
16	70	83 64	63	2.41	72	81 32	64	2 5	56	75 20	56	2 32
20	56	104 92	53	3 18	39	109 04	30	3 26	29	102 35	28	3 32
24	21	117 52	18	3 77	12	136 32	8	3 75	12	117 00	12	3.5
28	10	156 00	8	4 62	9	183 56	9	4 77	4	190 00	4	4 5
32	7	148 56	5	5 2	9	173 32	6	5 0	—	—	—	—
36	5	129.6	3	6 66	1	280 00	1	4 0	—	—	—	—
40	10	207 6	10	6 3	6	166 68	4	5 5	1	180 0	1	7 0
44	1	160 00	1	7 0	—	—						
48	4	202 0	4	7 5	1	200 00						
60	2	190 0	2	6 0	1	200 00						
80	3	280 00	2	8 0	1	280 00						

more variable individually (16.9) for mean diameters. The diameters of vessels observed in a normal heart tended to be somewhat (7 times) more alike relative to the total variation than in a single anginal or control heart.

The data in Table IX (Fig. 1) show that anginal vessels with *1* or *2* layers of muscle had slightly wider lumina and usually thinner walls than did equally muscular vessels in either other group, whereas normal vessels with 1 to 3 muscle layers were thicker walled and narrower than similar vessels in other groups. The lumina of anginal vessels with *4* to *5* muscle layers were narrower than the lumina of comparable vessels in the control group, and might be considered to be approximately equal to the lumina of comparable vessels of the normal group. Moreover, the wall thickness of these anginal vessels is usually greater than in either other group. The data in Table X show that the mean number of muscle layers for a given wall thickness varied little between each group, whereas the mean vessel diameter for a

First, the vessels in each group were compared as individual observations (Tables II, III, and IV). Thereafter, the three groups were compared. Each analysis answered an appropriate, different question in regard to the material studied. Professional statisticians assisted with these tests.

Results

Distribution of variates. Proportionately more larger vessels were found in the anginal group, and fewer vessels of the smallest measured diameters (40 to 76 μ) (Table II). The distribution of vessel sizes in the anginal group differed significantly from the distributions in the other two groups (chi square test; $p < 0.01$). The distributions of vessel sizes in the control and normal groups were not significantly different from one another ($p > 0.3$).

The vessels of the anginal group showed the greatest range of variation in wall thickness. There were fewer vessels with thin walls (8 μ) than in the control group, since fewer vessels of small diameter were present. The normal group had relatively more vessels of medium wall thickness (16 μ) than did the other two groups. The distributions were all significantly different from one another ($p < 0.01$ or < 0.001) (Table III).

The anginal group, in addition, showed a greater range of variation in the numbers of muscle layers, and included fewer thin-walled vessels with one muscle layer than did the control group. This is again due to the difference in distribution of diameters, as shown in Table II. There were relatively more vessels with intermediate numbers of muscle layers and fewer vessels with only one muscle layer in the normal group than in either of the other two groups. The distributions all differed significantly from one another ($p < .02$ or $< .001$) (Table IV).

Variance and means of the independent variates. Analysis of the measurements gives the statistics shown in Table V for the three groups. A calculation of the levels of significance between any two groups is given in Table VI.

With angina, the arteriolar vessels as a group were wider and thicker and had more muscle layers than the vessels in the other two groups. Moreover, they varied more in thickness and in numbers of muscle layers than in the other two groups. By way of contrast, normal vessels showed the least variation in diameter, thickness, and number of muscle layers. Normal vessels tended to have more muscle layers then control vessels, but fewer muscle layers than anginal vessels.

To investigate whether a large part of the differences found between the variates in the three groups was due to the fact that the hearts within each group were nonhomogeneous in respect to the variates measured, the variance found was analyzed for thickness and for diameter (see Tables VII and VIII).

The component of variance between hearts is 0.37, 0.24, and 0.27, respectively, for the anginal, control, and normal groups. Thus, the degree to which the thickress of vessels in any one heart displayed a distinct difference from that of vessels in another heart in the same group is 0.06, 0.06, and 0.15, respectively, for the anginal, control, and normal groups, as measured by intraclass correlation. Thus, there is a significant between-heart variation in the average wall thickness of the myocardial vessels, but the magnitude of the variation is small. The over-all variations in vessel thickness, which were greatest for anginal hearts, intermediate for control hearts, and least for normal hearts, are attributable almost entirely to variation within hearts, and there is a real difference between the three groups studied.

There are significant differences in diameter also between hearts (see Table VIII). The differences are less in the anginal and control hearts, but more in the normal hearts. The components of variance *between* hearts are 4.0, 3.5, and 16.9, and the intraclass correlations are 0.03, 0.03, and 0.21 for the anginal, control, and normal groups, respectively. Thus, the variation *between* hearts is very small in the anginal and control groups. The increasing variability of diameters as one moves from the normal group to the control group and then to the anginal group thus has nothing to do with the mean diameters for the samples of hearts chosen. In fact, the normal sample of hearts seems

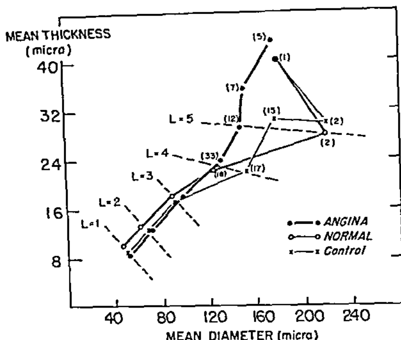


Fig. 1. The mean outside diameters of coronary arterioles are plotted against the mean wall thicknesses for the three groups studied, and are analyzed by comparison of the smooth muscle layers (*L*) present. Muscular hypertrophy of the larger coronary arterioles in the anginal group is evident.

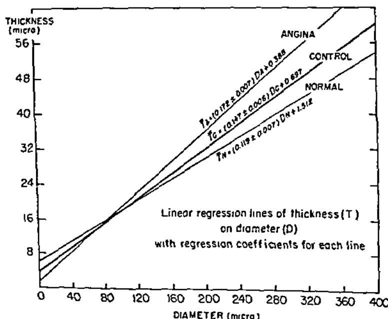


Fig. 2. By comparison of the linear regressions of outside arteriolar diameters plotted against wall thicknesses, coronary arterioles over 80 micra in outside diameter are found to be relatively thicker walled in the anginal group.

Table XI. *Ratio of mean vessel thickness on mean vessel diameter*

Number of muscle layers	*Anginal*	*Control*	*Normal*
1	163	173	205
2	182	180	211
3	182	190	201
4	181	144	180
5	200	174	127
6	235	136	—
7	245	222	222
8	236	—	—
14	286	—	—
Not counted	223	228	333

Table XII. *Interdependent correlations*

Correlation coefficients	*Anginal*	*Control*	*Normal*
Within hearts	812	786	807
Between hearts	652	614	684
Total	792	771	.790

given increment in thickness increased most rapidly in the control group and least rapidly in the anginal group. It may be deduced that anginal vessels showed a greater increment in muscularity and wall thickness per unit increase of diameter than did vessels of the other groups.

Arrays of the ratios of the means of thickness on mean diameter for different numbers of muscle layers clarify the changing relationship of these values between the three groups (see Table XI). It is apparent that in each array the increments in the numerical value of the ratio in the anginal and normal groups tend to a reciprocal relationship, whereas the values for the control group show an initial increment similar to that for the anginal group and then tend to revert to the pattern of decrement which characterizes the normal group.

It is obvious that there is some degree of correlation between vessel diameter and thickness, and the wall thickness and number of muscle layers. The correlation coefficients between diameter and thickness are given in Table XII. The correlations are highly significant. Thus, it appears likely that regressions which display the correlation of thickness on diameter in the three groups will give useful information about group characteristics (see Table XIII). It is noted that the between-heart regressions do not differ significantly from the within-heart regressions for each group, but the values are slightly less in each of the three groups. The three groups are all different significantly for total and within-heart regression values. They differ almost certainly, by internal consistency, for between-heart regression values, although only extremes (i.e., anginal and normal), differ significantly on a direct test. Even if the calculated regression lines (Fig. 2) are in fact nonlinear, the interpretation is qualitatively the same. It is apparent that small (40 to 80 μ) vessels in the normal group were thicker than vessels of the same diameter in the other groups. Small control vessels were also slightly thicker than small anginal vessels. The relationships of the lines became reversed with increasing diameter. Anginal vessels of diameters more than circa 80 μ were thicker than either control or normal vessels, and normal vessels became relatively thinner than the vessels of either of the other two groups.

Table XIII. *Regression coefficients of thickness on diameter*

Regression coefficients	*Anginal*	*Control*	*Normal*
Within hearts	0.172± 006	0.148± 006	0.124± .007
Between hearts	0 167±.046	0 134±.041	0.92± .035
Total	0.172±.007	0 147± 006	0.119± .007
Total regression through origin	0.186±.003	0 174±.003	0.187± .004
Regression constants for total regressions about means	+0.388	+0 697	+1.512

differences are due to chance, and the results are given to provide the reader with conclusions based on something beyond mere experience and opinion.

The risk of bias from a conscious or unconscious selection of material has not been ignored. Consideration of what unrelated selective influences might operate to influence the size, number, muscular thickness, and diameter of myocardial arterioles in one group more than another is inconclusive, because more factors are unknown than known, and the direction and extent of these influences cannot be adequately analyzed. From a knowledge of hospital admissions, autopsy rates, and procedures, we are of the opinion that the group sizes and relative case fatalities, choice and selection of material for study, and the plan of study of the anginal, control, and normal series were not free from bias. Despite the various uncertainties, a search for influences which would introduce an element of bias that would invalidate the findings has not discredited the plausible relationship observed between myocardial arteriolar alterations and angina pectoris.

Summary

The wall thicknesses, the numbers of muscle layers in the media, and the diameters of 20 arterial vessels of arteriolar size (40 to 280 μ) were measured or counted in microscopic sections of myocardium from each of 20 hearts taken from autopsied patients who had angina pectoris. The same measurements were made in 20 hearts from control subjects who were matched with the anginal group by age and sex, but who were without angina, and in each of 10 hearts from young subjects who had no significant vascular disease. The measurements and counts in the three groups were analyzed statistically to provide comparative data. The principal findings were: (1) There were fewer small and more large arterioles in the anginal group than in the other two groups. (2) Vessels from anginal hearts varied more in wall thickness and in numbers of muscle layers. (3) The regression lines of vessel thickness on vessel diameter were significantly different for each of the three groups. (4) Vessels from anginal hearts showed greater thickening of their walls with increase in diameter than that which occurred in either of the other groups. (5) Vessels of intermediate size from the anginal hearts were more muscular than comparable vessels from control hearts.

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Discussion

The arteriolar vessels studied from patients with angina pectoris had distinctive characteristics. There were relatively greater numbers of large vessels present than in the normal or control groups. Moreover, there was comparatively more variation in the size of such vessels in the myocardium of the anginal group. The smaller arteriolar vessels had relatively thinner walls than analogous vessels in the other groups, but with increments in diameter the vessels in the anginal group showed a greater increase in wall thickness than did vessels in the other groups. The arterioles of intermediate sizes from anginal hearts were as thick and muscular as vessels from normal hearts, and more muscular and thicker than vessels of equal size from control hearts. Still larger vessels of the anginal group were generally thicker and more muscular than vessels of equal size from the control or normal groups, but the number of such vessels measured was small.

We may suppose that in angina some of the smaller vessels (40 to 80 μ) in the myocardium had been entirely obliterated by replacement fibrosis of the myocardium, and others may have dilated out of the range of small vessel diameters. The small (40 to 80 μ) arterioles which remained in the anginal heart muscle were themselves generally somewhat dilated and, thus, had relatively thinner walls than similar vessels in other groups. Thus, the shift in the distribution may have been due to a combination of arteriolar obliteration and dilatation.

The distributions of vessel diameters were statistically skewed, being left asymmetrical. However, the distribution of *means* was considered to be within normal limits, and the levels of significance were, consequently, reasonably applicable. The significance of difference in variance should be treated with a little more caution in view of this asymmetry, although the "F" test used is robust for deviations from normality.

The figures for numbers of muscle layers are not considered to be very precise. Muscle cells are by no means disposed in perfectly concentric layers, but intermingle to some extent. However, the same sources of error were present in both control and anginal vessels. Thus, the difference in muscularity of arteriolar vessels in these groups is considered to be real, at least in a relative sense. Normal vessels had a rather more orderly media, so that the estimation of muscle cell layers was rather easier to make. When significant numbers of vessels, e.g., over 10, were present in the plotted regressions of each group, normal vessels were found to be as muscular as, or more muscular than, anginal vessels. This suggests that the essential difference between the anginal vessels and control vessels is that anginal vessels remained more reactive or more capable of muscle contraction than did control vessels. Consequently, a reason for the development of angina pectoris is that the arteriolar vascular bed retains constrictive reactivity in the face of a seriously diminished arterial blood supply. It may not be true that when the arteriolar bed dilates it is incapable of delivering the same amount of blood as in other arteriosclerotic hearts.

The three populations of arterioles overlap in some respects, but the three groups show differences in the degrees of association and the rates of change of association of the variates. Our findings tend to support the accepted hypothesis that angina pectoris is due to vascular spasm and, hence, may be relieved by vasodilators that act directly on coronary vessels,[16,17] thus increasing blood flow,[4] possibly partly via collateral channels.[18]

This study represents a limited application of experimental histopathology to myocardial arterioles, which has involved measuring these vessels for, apparently, the first time. The usual evolution of medical knowledge that comprises the stages of observation, measurement, and mathematical analysis has been followed, but no claim of absolute accuracy, great precision, certainty of proof, or universal application of the results is intended. The complex statistical analyses employed have not been made to prove that differences exist or that the simple measurements recorded are conclusive evidence of arteriolar alterations. The tests have evaluated the probability that the observed

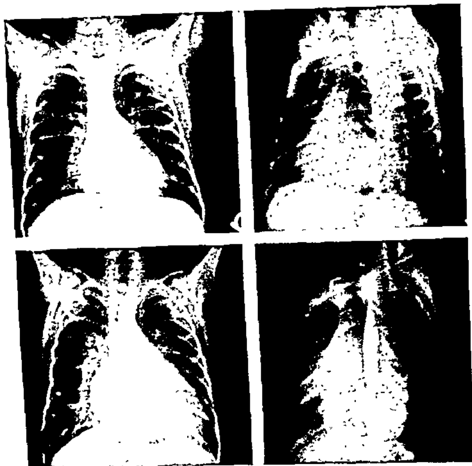


Fig. 1. Roentgenograms of chest of boy with progeria taken in posterior-anterior and left anterior oblique views. The upper films were obtained when he was 10½ years old; the lower ones were obtained when he was 12 years old, 3½ months prior to death.

Because of his small size, peculiar external appearance, and general weakness, the patient was restricted in his physical and social activity, although his interests were normal for his chronological age. Two younger siblings were entirely normal.

History of the present illness. A persistent cough was first noted in July, 1958, when the patient was 12 years old. Coughing occurred mainly at night and was relieved by the use of additional pillows during sleep. Loss of weight, easy fatigability, shortness of breath with exertion, and general apathy became progressively more apparent. In September, 1958, a roentgenogram of the chest (Fig. 1) demonstrated gross cardiomegaly. Hospitalization for the purpose of digitalization was advised.

PHYSICAL EXAMINATION. On admission, physical examination again revealed the classic external appearance associated with progeria. The pulse rate was 140 per minute; the respiratory rate was 42 per minute at rest. The peripheral arteries were readily palpable as hard cord-like structures in all four extremities. A blood pressure could be obtained by palpation only and was 78 mm. Hg in both arms. The heart sounds had a variable quality and were not of great intensity. A diastolic gallop rhythm was present at the apex. After he was digitalized, a high-pitched, somewhat squeaky systolic murmur was audible to the left of the lower sternum. The liver was not grossly enlarged. The lungs were normal to auscultation.

LABORATORY STUDIES. On admission, the hemoglobin level was 12 Gm. per cent; the total white blood cell count was 16,000 with a normal differential. An electrocardiogram (Fig. 2) demonstrated a sinus tachycardia. The QRS complexes demonstrated changes which indicated apical and septal myocardial fibrosis. In addition, the S-T and T-wave changes usually associated with left ventricular enlargement were present. X-ray (Fig. 1) and fluoroscopic examination of the chest revealed a moderate degree of cardiac enlargement, with specific evidence of left ventricular hypertrophy. On barium swallow, there was also evidence of left atrial enlargement in the roentgenogram taken in the right anterior oblique view.

HOSPITAL COURSE. Approximately three times the usual digitalizing dose of digitalis, based upon total

Cardiovascular manifestations in progeria. Report of clinical and pathologic findings in *a patient with severe arteriosclerotic heart disease* and aortic stenosis

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Progeria is a rare syndrome of congenital dwarfism of unknown etiology. Thirty-two typical cases have been reported to date, including the original clinical note by Hutchinson in 1886, and the classic description of Gilford in 1897.[1-36] Retardation of growth, hypermetabolism, abnormalities of the skin and appendages, and minor skeletal changes with normal bone age are the essential features of progeria. The usual cause of death is generalized arteriosclerosis with cardiac complications during late childhood and adolescence. Postmortem examinations have been described in detail in 7 instances,[2,5,19,22,27,30,33] and the findings in an unpublished case were summarized by Thomson and Forfar.[21]

A patient with progeria, whose case was previously described during life by Album and Hope,[35] is reported upon here after postmortem examination and with special consideration of alterations in the cardiovascular system. The literature has been reviewed in an attempt to establish the natural course of clinical events in the development of the cardiac complications of progeria.

Case report

F. F., a 12½-year-old white boy, with the typical external appearance of a patient with progeria,[11] died at home on Dec. 24, 1958, after a 6-month interval of worsening congestive heart failure.

Past medical history. The mother's pregnancy was uneventful. The patient weighed 6½ pounds at birth on Sept. 19, 1946. Aside from an episode of acute arthritis which involved the left hip, the infant was considered to be normal until the age of 9 months. At that time he lost what had appeared to be a healthy crop of hair. When the infant first walked at 14 months, his joints were noted to be stiff. When he was 15 months old, the fingernails and toenails were observed to be hard, yellow, and brittle; the skin was thin and taut. During hospitalization of the patient for study at the Hospital of the University of Pennsylvania when he was 2 years old, the diagnosis of progeria was obvious. The blood pressure was noted to be 95/50 mm. Hg when he was 4 years old, at which time he was 37 inches tall and weighed 25 pounds. A mid-precordial systolic murmur was noted when he was 4 years old.

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years; the average was 14 years. Nine of the 14 who died were males.

Twenty observations were made concerning the presence of a cardiac murmur in 8 boys and 4 girls. In these 12 patients the presence of a murmur was noted when 3 were under 5 years of age, when 5 were between 5 and 10 years of age, when 7 were between 10 and 15 years of age, when 3 were between 15 and 20 years of age, and when 2 were over 20 years of age.

Thirty-two determinations of blood pressure were reported in the literature among 20 patients with progeria whose ages ranged between 2 and 27 years. The individual determinations are recorded in Table I. After 6 years of age, the mean systolic pressure of the group was more than one standard deviation above the mean systolic pressure of normal individuals, and the mean diastolic pressure of the group was more than two standard



Fig. 3. Aortic valve, showing rigid calcific stenosis. Note calcific nodules on inner surfaces of valve cusps.

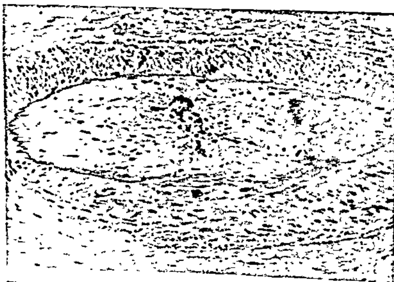
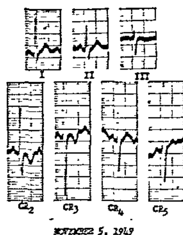


Fig. 4. Major branch of coronary artery completely occluded by process of subintimal fibrosis. Hematoxylin and eosin, X40.



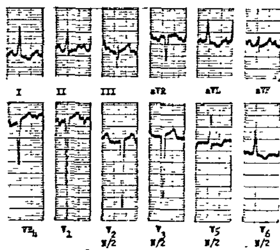


Fig. 2. Electrocardiograms of patient with progeria. The upper tracing was recorded when he was 3 years old, the lower one was recorded when he was 12 years old, 4 months prior to death.

body weight, was administered before any change in the cardiac or respiratory rates was noted. A slowing of the cardiac rate to 110 per minute was eventually achieved. The patient was finally discharged on oral Digalen, 8 minims per day.

SUBSEQUENT COURSE. Multiple conventional measures for the symptomatic treatment of congestive heart failure were employed during the next 6 months while the patient was cared for at home. Aside from digitalis, these included the use of diuretics orally and by the parenteral route, a low-salt diet, and the use of sedatives. The course was a relentlessly downhill one, and the patient died during an intercurrent gastrointestinal infection.

Postmortem examination.

GROSS FINDINGS. Apart from atrophy of the skin and the appendages and degenerative osteoarthritis, the most striking changes were noted to involve the cardiovascular system. A greatly distended inferior vena cava emptied into a dilated right atrial chamber whose walls were hypertrophied. Similarly, the chambers of the right ventricle and the left atrium were dilated, and the walls of these chambers as well as those of the left ventricle were hypertrophied, except as noted below. Endocardial thickening was pronounced over the septum of the right ventricle and throughout the left atrium. Deformities were noted in both mitral and aortic valves. The anterior cusp of the mitral valve was calcified; the chordae tendineae were thickened and shortened. The papillary muscles, likewise, were thickened. No stenosis of the mitral valve was noted. The aortic valve (Fig. 3) was markedly calcified and the orifice was stenotic. Deposits of calcium were seen in the aorta just above the margins of the cusps. Multiple atheromatous calcific plaques involved the aorta throughout its entire intrathoracic and intra-abdominal course.

The myocardium at the apex of the left ventricle was very thin. Tissue which comprised the anterior surface cut with moderate resistance; a characteristic mahogany-brown appearance was altered by streaks of white scar tissue. Elsewhere, the myocardium, notably the interventricular septum, showed a red-yellow mottling on section.

The lumen of the left coronary artery, for a distance of 1 cm. from its ostium, was completely occluded by gritty atheromatous material. The luminal caliber of the remainder of this vessel and that of the entire right coronary artery were greatly reduced by subintimal atheromatous deposits. The pulmonary artery showed marked arteriosclerosis.

MICROSCOPIC EXAMINATION. Microscopically, a proximal segment of a coronary artery revealed the extent to which luminal caliber had been compromised by subintimal fibrosis (Fig. 4). In addition, the myocardium, in large focal areas, was replaced by dense irregular islands of collagenous connective tissue (Fig. 5). Other areas showed recent ischemic myocardial degeneration unaccompanied by an acute inflammatory cell infiltrate (Fig. 6). Large and medium-sized pulmonary arteries showed advanced subintimal fibrosis and a moderate degree of medial hypertrophy.

ANATOMIC DIAGNOSIS. Progeria with calcific aortic stenosis; coronary artery sclerosis with occlusion and interstitial myocardial fibrosis; arteriosclerosis of the pulmonary arteries.

Review of literature

Thirty-two typical cases of progeria, including the present one, have been reported since 1886.[1-34] Specific mention of the cardiovascular system was made in most of the 31 case reports available to us. Eighteen of the 32 patients were living when reported upon. The age range in this group varied from 2 to 26 years; the average was 9 years. Nine of the 18 living patients were males. Fourteen patients were reported upon after they had died. The age at death ranged from 7 to 27

The tracing of the 7-year-old girl was reported to show evidence of right ventricular preponderance 1 year prior to death. No other definite abnormalities were described.

Comments in regard to the status of the peripheral arteries were made in 8 instances, and the funduscopic examination was reported in 4 instances. No consistent relationship was found between the detection of clinical evidence of peripheral arterial disease and the occurrence of the sequelae of arteriosclerosis, e.g., cerebral vascular accidents and angina pectoris.

Multiple determinations of total serum cholesterol were reported in 13 patients who were between 2 and 19 years of age. In every one of the 13 patients, at least one determination was higher than 184 mg. per cent, which is the mean total serum cholesterol value for normal children, according to Offenkrantz and Karshan.[40] Eight of the 13 patients had values more than two standard deviations above this normal mean value. All of the 8 patients with elevated values of serum cholesterol were over 4 years of age. Five of the 13 patients had normal levels of cholesterol; 3 were under 4 years of age, and 2 were over 4 years of age. A 10-year-old girl in whom no determination of cholesterol had been made demonstrated xanthomatous skin lesions over the left lower quadrant of the abdomen.[15]

Death was apparently due to coronary artery disease in 12 of the 14 patients who died. The average age at death was 14 years; it was 15 years for the 9 boys and 11 years for the 5 girls. In 8 of 12 patients who died of heart disease the presence of a heart murmur had been recognized 3 to 9 years prior to their deaths. Among the 14 patients whose deaths were reported, 5 of the 6 patients with angina pectoris were males. The symptoms of angina pectoris preceded death by as long as 4 years in 6 instances. A 7-year-old girl, an 8-year-old boy, and a 9-year-old boy had anginal symptoms for less than 1 year prior to death. Boys of 11, 17, and 18 years had angina pectoris for 2, 3, and 4 years, respectively, prior to death. Severe congestive heart failure accompanied the terminal episode in at least 2 patients.

The age range of the 8 patients whose autopsies have been reported was 7 to 27 years; the average age was 14 years. The same age range prevails in the group of 6 patients in whom no autopsy was performed. Only 2 of the 8 patients subjected to postmortem examinations were females. The 6 males died of arteriosclerotic heart disease. In 3 of 5 patients, thickening of the aortic valve leaflets was most prominent at the valve bases. In 4 of these 5 the aortic valves were calcified. In 4 of the 8 autopsy descriptions, the mitral valve was reported to be involved by atheromatous changes. The chordae tendineae were shortened in 3 instances. Endocardial involvement was absent in the 9- and 11-year-old girls.

Of the 8 autopsied patients, all but the 9-year-old girl had thickening of the coronary arteries, and most had calcification of the coronary arteries. The coronary ostia were occluded or nearly occluded in 5 patients. All had marked atheromatosis of the aorta, with involvement of major arterial branches in some instances. Nephro-

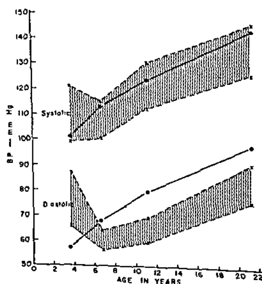


Fig. 7. The systemic blood pressure in progeria. The solid lines which connect the black dots represent the mean systolic and diastolic blood pressures in 20 cases of progeria. The 4 dots in each line locate the average age and blood pressures of cases in the age groups 2-5 years, 5-10 years, 10-15 years, and over 15 years. Seven of the cases are included in more than one age group. The shaded areas include two standard deviations above the mean normal values according to the published data of Allen-Williams[19] and Graham and associates.[28]

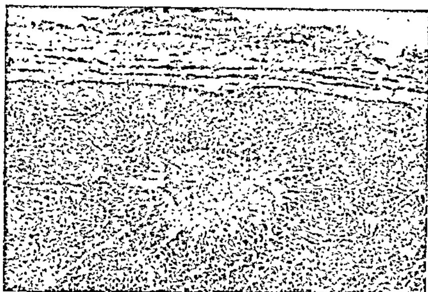


Fig. 5. Focal area of myocardial scarring. Hematoxylin and eosin, ×10.



Fig. *6.* Recent ischemic myocardial degeneration. Note ghost cells and absence of fibrosis. Hematoxylin and eosin, ×40.

deviations above the mean diastolic pressure of normal individuals. These relationships are illustrated in Fig. 7.

Cardiac enlargement was noted in 8 of the 31 reported cases. This finding was proved by x-ray examination in 5 instances. In only 1 patient, a 12-year-old boy, was the heart enlarged in the absence of a cardiac murmur, but in this instance the blood pressure was elevated to a level of 140/90 mm. Hg. Cardiac enlargement was present in 3 other patients with elevated blood pressures, but in each instance a heart murmur was also present. Cardiac enlargement was not reported in the absence of either hypertension or a cardiac murmur.

Electrocardiograms were obtained in 13 of the 31 patients, but only one of these electrocardiograms was reproduced. In 3 instances the tracings were reported to show evidence of myocardial infarction.

Cardiac murmurs	*Cardiac enlargement*	*ECG*	*Cholesterol (mg./100 c.c.)*	*Age at death*	*Miscellaneous comments*
—	—	—	—	—	—
—	—	—	—	—	—
Soft apical and loud low-pitched basilar systolic	Slight	—	—	17 yr. (no autopsy)	Died of acute coronary artery disease
Apical and harsh basal systolic	Slight	—	—	—	Tortuous temporal arteries
Apical and harsh basal systolic	Slight	—	—	18 yr. (autopsy)	Died of acute coronary artery disease
Apical and harsh basal systolic	—	—			
—	—	—	—	15 yr. (no autopsy)	—
None	None	—	—	—	—
None	None	—	—	—	—
None	None	—	—	—	—
None	None	—	—	—	—
Systolic, apical and basilar	None	—	—	—	—
Systolic and diastolic, apical and basilar	Slight enlargement to right by x-ray	Possible old infarct	—	27 yr. (autopsy)	Died of congestive heart failure
—	—	—	—	21 yr. (autopsy)	Died of acute coronary artery disease
None	None	—	—	—	—
Present	—	—	—	—	—
Presystolic apical murmur with thrill and apical systolic	None	Right ventricular preponderance	—	8 yr. (no autopsy)	Thick, tortuous peripheral arteries. Hemiplegia
—	None	—	—	—	—
—	Slight enlargement on x-ray	—	—	—	—
None	None	—	—	—	—
Loud apical systolic	None	—	270	—	—
—	—	—	—	—	—
—	—	Normal	—	—	Xanthomata on left lower quadrant of abdomen
Apical systolic	Slight	—	—	—	—
None	None	Normal	328	—	—
None	None on x-ray	—	—	—	—
None	None on x-ray	—	—	—	—
—	—	—	—	—	—

Table 1. Summary of cardiovascular manifestations in 32 patients with progeria

Case number	Author	Age (yr.)	Sex	Cardiac symptoms	BP (mm. Hg)
1.	Hutchinson and Gilford[1,2,4]	3.5	M	—	—
		14		Very active	—
		15.5		Easily tired; paroxysmal nocturnal dyspnea. Substernal pain on running. Sweating attacks	—
2.	Gilford[2-4]	14	M	Exertional dyspnea. Attacks of epigastric pain	—
		17		Exertional dyspnea. Pain in left breast, radiating to left arm	—
		18		Orthopnea. Pain in left breast, radiating to left arm	—
3.	Variot and Piremeau[5]	15	F	—	—
4.	Manschot[22] (Schipper)	3.5	M	None	—
		10		None	—
		12.5		None	110/85
		16		None	—
		18		None	132/90
		26-27		Extreme dyspnea	180/120
5.	Orricio and Strada[5]	19	M	—	—
		21			
6.	Nasso[6]	4	F	—	—
7.	Curtin and Kotzen[7]	4	F	—	—
		7-8		Dyspneic episodes. Attacks of precordial pain	105/54
8.	Strunz[8]	4.5	F	—	—
9.	Thiers and Nahan[9]	19	M	—	—
10.	Schiff[10]	6.5	F	None	105/55
11.	Exchaquet[11,12]	13.9	F	—	—
12.	Broc, et al.[13]	11	M	—	—
13.	Popek and Hadlik[14]	8	F	—	105/70
14.	Mitchell and Goltman[15]	10	F	Easily fatigued	136/86
15.	Zeder[16]	5	M	—	120/80
16.	Schondel[17,18]	5	F	None	—
		12		None	—
		26		—	—

Cardiac murmurs	*Cardiac enlargement*	*ECG*	*Cholesterol (mg./100 c.c.)*	*Age at death*	*Miscellaneous comments*
None	—	Normal	—	—	—
None	—	—	170 to 300	7 yr. (autopsy)	Acute and old myocardial infarctions
None	—	—			
None	None	Normal	—	—	—
None	None	Normal	—	—	—
—	—	Infarct?	—	8 yr. (no autopsy)	Died of myocardial infarction
Systolic in 3rd left intercostal space	None on x-ray	Normal	275	—	—
—	—	—	260	—	—
Apical systolic	Slight enlargement on x-ray	—	—	—	—
—	—	—	—	13.5 yr. (no autopsy)	Died of myocardial infarction
None	None on x-ray	Normal	185	—	
—	—	Normal	—		
None	None	—	—	9 yr. (autopsy)	Convulsions for 10 hr. prior to death
None	None	—	200	—	—
None	Marked enlargement on x-ray	—	—	—	Died of myocardial infarction. Cerebral vascular accident prior to death
None	Same	—	—	—	
None	Same	—	0	16 yr. (no autopsy)	
None	None	—	294	—	—
Soft systolic precordial	—	Normal	—	—	—
Harsh systolic	—	Normal	—	—	—
Soft systolic blow	—	Normal	240-287	—	—
Harsh apical systolic	—	Infarction	—	—	—
Harsh apical systolic	—	Acute infarction	—	11.8 yr. (autopsy)	Died of myocardial infarction
—	—	—	—	—	—
—	—	—	218	—	—
Loud apical systolic	—	—	180	—	—
Loud apical systolic	—	—	—	—	—

Nearly 40 per cent of the patients with progeria develop cardiac murmurs. These usually appear after the patient is 5 years old, but the characteristic organic nature of these murmurs may not be appreciated until after the patient is 10 years old, presumably when the atherosclerosis becomes more severe. Beyond the age of 10 years, the incidence of cardiac murmurs increases significantly. Murmurs in patients with progeria are probably due to atherosclerosis which involves principally the anterior cusp of the mitral valve and the proximal portions of the aortic valve cusps. Atherosclerotic involvement of the outflow tract of the left ventricle, with extension to the adjacent areas of the ascending aorta, may also produce cardiac murmurs.

Diastolic systemic hypertension is a

Table I. Summary of cardiovascular manifestations in 32 patients with progeria—Cont'd

Case number	*Author*	*Age (yr.)*	*Sex*	*Cardiac symptoms*	*BP (mm. Hg)*
17.	Talbot, et al.[19]	6.4	M	—	125/85
		6.5		Attacks of orthopnea. Epigastric pain	120/80
		7.5		—	100/60
18.	Schwartz and Cooke[20,21]	4.8	M	—	120/80
		6.5		—	—
		7.5-8.4		Attacks of chest pain	110/70
19.	Thomson and Forfar[21]	4.5	M	—	106/64
20.	Hughs[23]	5	M	—	104/74
21.	Cooke[24]	6	F	—	90/–
		13.5		Paroxysmal nocturnal dyspnea and chest pain 2 days prior to death	—
22.	Gabr[25-27]	4	F	—	108/25
		5.7		—	110/60
		9.0		—	—
23.	Mostafa and Gabr[28]	2.3	F	—	95/60
24.	Doub[29]	10	M	None	—
		12		—	140/90
		16.5		Severe chest pain	—
25.	Muzzo and Alonso[29]	8	F	—	—
26.	Atkins[30]	2.9	M	—	90/50
		5		—	90/60
		8.5		—	125/80
		9.9		Episodes of nausea. Paroxysmal nocturnal dyspnea	92/50
		11.4		Severe congestive heart failure. Chest and abdominal pain	120/80
27.	Plunkett, et al.[31]	5	M	None	—
		8		—	80/40
		19		—	—
		21		None	—

sclerosis was present in 7 patients. Only in our own patient were atheromata of the pulmonary artery described.

Discussion

The cause of progeria remains obscure. Its presence is usually recognized during the second year of life. Those patients who reach the third decade rarely exceed the average weight and height of a 6-year-old child. Except for the externally visible abnormalities, most of the signs and symptoms as well as the mechanism of death result from the complications of arteriosclerosis. These clinical manifestations, which usually do not appear until after the patient is 6 years old, are cardiac murmurs, systemic hypertension, angina pectoris, myocardial infarction, and congestive heart failure.

Cardiac murmurs	Cardiac enlargement	ECG	Cholesterol (mg /100 c.c.)	Age at death	Miscellaneous comments
None	—	Normal	225-240	—	—
Apical systolic	None on x-ray	Normal	270-291	11 yr. (autopsy)	Post-traumatic epidural hematoma
None	None	—	—	—	—
None	None	Normal	199	—	—
None	None	Normal	144	—	—
Systolic, mid-precordial	None	Normal	160-178	—	—
Systolic, mid-precordial	None on x-ray	Normal	—	—	—
Squeaky; systolic lower left sternal border	Moderate enlargement on x-ray	Left ventricular hypertrophy	—	12 yr. (autopsy)	Died of congestive heart failure
—	—	Normal	—	—	—

fectiveness of large doses of digitalis in our patient may be attributed to the pathologic alterations, namely, the combination of myocardial infarction and aortic stenosis. It is also possible that the hypermetabolic state of patients with progeria may increase the requirement for digitalis for therapeutic effects. Although the hypermetabolism is usually not thyrotoxic in nature, attempts have been made to reduce the total oxygen need with antithyroid therapy.[19,30,32,34] Even though only limited success has been achieved with antithyroid therapy in compensated patients with progeria, this approach would be worthy of further trial in the presence of congestive heart failure.

Because of the positive correlation between atherosclerosis and hypercholesterolemia,[41] several cases of progeria have been studied with regard to abnormalities in lipid metabolism. In one of these instances, beta-lipoproteins[32] were found to be elevated, and in another the atherogenic index of Gofman,[33] based on the ultracentrifugal properties of lipoproteins, was also elevated. Since the majority of patients with progeria who are over 4 years of age have elevated levels of total serum cholesterol, further study of these rare patients may contribute to the understanding of the role which cholesterol plays in the etiology of atherosclerosis.

Summary

The case of a 12-year-old boy with progeria, which was previously reported during his lifetime, is presented again, but this time with postmortem findings and with emphasis on the cardiovascular abnormalities. Death resulted from coronary artery atheromatosis and insufficiency, interstitial myocardial fibrosis, and calcific aortic stenosis.

The 31 other typical cases of progeria reported in the literature since 1886 are reviewed with respect to the clinical and pathologic findings in the cardiovascular system. From this review, the natural course of cardiovascular events in progeria has been reconstructed. Cardiac murmurs usually appear after the patients are 5 years old; subsequently, diastolic systemic hypertension, cardiomegaly, and hypercholesterolemia develop. Death from cardiac complications at an average age of 14 years is usually preceded by angina pectoris, myocardial infarction, or congestive heart failure.

REFERENCES

1. Hutchinson, J.: Congenital absence of hair and mammary glands with atrophic condition of

Table I. Summary of cardiovascular manifestations in 32 patients with progeria—Cont'd

Case	*Author*	*Age*	*Sex*	*Cardiac symptoms*	*BP (mm. Hg)*
28.	Keay, et al.[32]	3	M	—	110/64
29.	Rosenthal, et al.[33]	11	F	—	100/60
30.	Steinberg, et al.[34]	5.5	M	—	—
31.	Album and Hope[35]; Makous, et al.	3	M	None	85/60
		4		None	92/54
		5		None	120/80
		10		None	130/76
		11		Exertional dyspnea	101/79
32.	Outon[36]	5.9	M	—	135/60

common cardiovascular complication in progeria; it may appear before the patient is 5 years old, but usually is not definite until after he is 6 years old. Accompanying nephrosclerosis is not uniformly present. Cardiac enlargement does not always accompany the elevated blood pressure; when it does, a heart murmur is frequently present.

Angina pectoris, another common manifestation of cardiovascular involvement in progeria, rarely appears before the patient is 6 years old. Death usually occurs within 4 years after the onset of angina pectoris, as a result of acute coronary insufficiency either with or without myocardial infarction. The manifestations of congestive heart failure may precede death.

Electrocardiographic evidences of myocardial infarction are not common in progeria. Coronary atherosclerosis is usually extensive, as is the atherosclerotic involvement of the aorta. Occlusion of the right coronary ostium is especially common. Arteriosclerosis elsewhere is not necessarily extensive or advanced, but is usually present.

The detection of significant asymptomatic arteriosclerosis in children with progeria is as difficult and unsatisfactory as it is in adults. Because early coronary artery atherosclerosis has apparently been minimal, stress tests, including exercise or the use of drugs, such as epinephrine, have not been found to cause abnormal responses in several asymptomatic children with progeria.[6,16,32] Symptomatic coronary artery disease may initially present gastrointestinal symptoms. Eventually, the more typical pattern of angina pectoris or pain characteristic of coronary artery insufficiency appears. The resultant electrocardiographic changes are frequently nonspecific, but, occasionally, a typical pattern of myocardial infarction may develop. Fluoroscopic visualization of calcified valve leaflets should be an additional diagnostic aid.

The results of treatment of the cardiovascular complications of progeria have been uniformly unsatisfactory. Treatment of coronary artery insufficiency and heart failure is at present primarily palliative. The use of coronary vasodilators may fail to help even transiently because fixed coronary ostial stenosis is probably responsible for much of the coronary artery insufficiency. Digitalis, a low-sodium diet, and the use of diuretics comprise the basic treatment of congestive heart failure in progeria, as in other conditions complicated by congestive heart failure. The inef-

Experimental and laboratory reports

The circulatory effects of squatting

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William Hunter[1] noted in 1784, that cyanotic patients obtained relief from faintness by assuming the posture which we now call "squatting." In squatting, the body is brought closer to foot level by flexing the hips and knees, and the trunk is arched forward so that the knees are brought up to the chest. Taussig[2] pointed out that cyanotic children with Fallot's tetralogy often assume this posture after exercise and feel less breathless and less faint as a result. Campbell and Suzman[3] reported that 80 per cent of their patients with Fallot's tetralogy squatted, and a history of squatting has also been reported in patients with tricuspid atresia,[4] transposition of the great vessels,[3] and pulmonary hypertension with ventricular septal defect.[5]

The mechanism by which squatting relieves breathlessness and faintness in some patients with cyanotic congenital heart disease is not known. Taussig noted that most patients who squatted had a low pulmonary blood flow, and Lurie[6] showed the deleterious effect on arterial oxygen saturation of the pooling of blood in the legs of a patient with Fallot's tetralogy. He found that elastic bandages around the legs prevented this fall in oxygen saturation caused by standing, and postulated that squatting increased venous return and cardiac output and raised the oxygen saturation in arterial blood by increasing mixed venous saturation. More recently, Brotmacher[7] studied patients who squatted to relieve breathlessness. During cardiac catheterization they simulated squatting by pulling their knees up to their chests. This maneuver produced no changes in systemic or pulmonary blood flow. He also studied patients who squatted from the standing position after exercise,[8] and found that the arterial oxygen saturation, as measured by ear oximetry, returned to its resting value more rapidly if the patient squatted during the recovery period. He, like Lurie, thought that an increase in oxygen saturation in the mixed venous blood was responsible for these results.

Sharpey-Schafer,[9] in a study of normal subjects, found that squatting caused an increase in systemic arterial pressure that was followed by bradycardia. He suggested that squatting increased cardiac output by increasing venous return, and that the bradycardia was secondary to baroreceptor activity. He also thought that squatting caused a small, immediate increase in arterial resistance, because of removal of the distending force of gravity on the systemic arterial bed. He suggested that the weight of the column of blood in the arteries below the heart distends the bed in the upright posture, and that squatting removes this force and narrows the ar-

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by the manometric method of Van Slyke and Neill. In the other patients with Fallot's tetralogy, arterial oxygen saturation was measured with a continuously recording ear oximeter.* The oximeter was calibrated by comparison with samples of arterial blood analyzed by the manometric method of Van Slyke and Neill and found to be accurate to within 5 per cent.

Indicator-dilution curves were obtained in 2 of the normal subjects and in 4 patients with Fallot's tetralogy with a Norman NEP ear oximeter[10] and a Leeds Northrup potentiometer recorder. Duplicate determinations of cardiac output and "central blood volume" were made in the normal subjects in the squatting and standing positions. A measured amount of Coomassie blue dye was injected through a catheter into the superior vena cava, and a sample of arterial blood was taken 2 minutes after the curve was inscribed, for spectrophotometric determination of dye concentration. Mean circulation time was measured from the curves, and cardiac output and "central blood volume" were calculated. The ear oximeter has been shown in this laboratory to have a linear response to increasing concentration of Coomassie blue dye up to 100 mg. per liter, and comparisons with the cardiac output measured by the direct Fick method have shown agreement within 10 per cent. Cardiac output and "central blood volume" could not be measured in this way in the patients with Fallot's tetralogy because of the right-to-left shunt, and only qualitative curves could be obtained. In the patients with Fallot's tetralogy, Cardiogreen dye was used, and the site of injection was again in the superior vena cava. An indication of the volume of blood shunted from right to left was obtained from the size of the first peak of the dye curve. In Patients 5 and 6, dye curves were obtained in the squatting and standing positions. In Patients 4 and 7, dye curves were obtained in the lying and squat-lying positions, and in Patient 4, arterial and right atrial samples were taken in the squatting and standing positions.

Exercise. In 7 of the patients with Fallot's tetralogy the arterial oxygen saturation was measured by ear oximetry during recovery from exercise on a motor-driven treadmill. After a short period of exercise, sufficient to reduce the saturation or produce mild breathlessness, the treadmill was stopped and the patient was asked to squat. After 20 to 30 seconds the patient stood up and the process of alternate squatting and standing was repeated. If the upward trend of the oximetric record during squatting reversed when the patient stood up, and the saturation fell, we considered that squatting had increased the rate of recovery of saturation and consequently benefited the patient. The appearance time of any rise in saturation on squatting was noted, and the presence of a fall in saturation immediately after squatting was looked for.

Squat-lying. Four normal subjects and 3 patients with Fallot's tetralogy (Patients 4, 7, and 14) squatted in the lying position in the manner described by Brotmacher.[7] They pulled their knees up to their chests, and measurements were made in both lying and squat-lying positions. In Patients 4 and 7, dye-dilution curves were recorded in both postures.

Swimming pool. The effects of squatting in water at 75°F. in a swimming pool were studied in 5 normal subjects. The subjects squatted and stood at the side of the pool and then repeated the maneuver in water up to a constant level at the umbilicus or the nipple. To do this, the subject stood in water of the appropriate depth and then squatted on a chair in the pool. Blood pressure and pulse rate were measured by auscultation in 4 and directly in 1.

Results

A continuous tracing of arterial pressure of a normal subject during squatting and standing is shown in Fig. 1,*A*; similar tracings were obtained in 7 other normal subjects. The measurements of blood pressure and pulse rate in the steady state are shown in Table II. In 4 of these subjects, tracings were also obtained in the squat-lying position. All subjects had an immediate increase in systolic, diastolic, and pulse pressures when they squatted from the standing position. About 4 beats after squatting there was a bradycardia, which is interpreted as a baroreceptor response to the rise in pulse pressure. The

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Table I. Clinical details in 14 patients with Fallot's tetralogy

Patient	*Age (yr.)*	*Sex*	*History of squatting*	*Level of stenosis**	*Arterial saturation†*	*Aortic pressure (mm. Hg)*	*Dye curve showing R-L shunt*	*Remarks*
1.	7	M	+		90	115/67	+	Operation
2.	16	F	−	V	83			
3.	17	M	+	I	49‡			Operation
4.	18	M	+	V	92	122/80	+	Previous Blalock
5.	23	F	−	I	92		+	Operation
6.	25	F	−	V	87		+	Operation
7.	38	F	+	I	92	122/68	+	Previous Blalock
8.	5	F	−		69	112/85		Previous Blalock
9.	6	M	−	I				Operation
10.	9	F	+	I	88	100/62		Operation
11.	16	M	−	I	97	120/75		
12.	22	M	−	V	94			Operation
13.	22	M	−	I	83	119/24	+	Previous Blalock (PA 107/37 mm. Hg)
14.	23	M	+	I	83	100/85		Operation

*V: Valvular. I Infundibular
†At cardiac catheterization
‡Sitting

terial bed. When he studied squatting in patients with congestive heart failure, he found only a small increase in blood pressure and no bradycardia. He thought that a failing heart could not respond to increased filling with an increase in output, and he contrasted the effects of squatting with those of the Valsalva maneuver, which decreases venous return. He suggested that patients who had a square-wave response to the Valsalva maneuver had little change in blood pressure or pulse rate when they squatted.

We studied the effects of squatting in normal subjects and in patients with congenital heart disease, in an attempt to explain how squatting increases arterial oxygen saturation in some patients and thus provides symptomatic relief.

Methods

We studied 14 patients with Fallot's tetralogy who were cyanotic either at rest or after exercise, and 14 acyanotic subjects (11 normal subjects and 3 with atrial septal defect). The subjects squatted from either the standing or the lying position (squat-lying) at rest or after exercise, and 5 of the normal subjects squatted in a swimming pool. The diagnosis of Fallot's tetralogy was confirmed by cardiac catheterization, angiocardiography, or operation; clinical details are shown in Table I. The patients with atrial septal defect had large left-to-right shunts with pulmonary-to-systemic flow ratios of 3 to 1 or more. The diagnosis was confirmed by cardiac catheterization and operation.

In the acyanotic subjects, a continuous tracing of systemic arterial pressure was obtained with a Statham strain gauge connected to a polyethylene catheter inserted percutaneously into the brachial artery in all except 4 of those who were studied in the swimming pool. Blood pressure was measured directly in 1 subject and by auscultation in the other 4 subjects studied in the swimming pool. During changes in posture the strain gauge was held at the level of the sternal angle. Pulse rate and blood pressure in the steady state were measured at least 30 seconds after a change in posture. In the patients with Fallot's tetralogy, arterial pressure was measured in a similar manner in Patients 2 through 7. In the other patients, pulse rate alone was measured.

Arterial oxygen saturation was measured in the squatting and standing positions in all the patients with Fallot's tetralogy except Patient 6. In Patients 2, 3, 4, 5, and 7, samples of arterial blood were analyzed

systolic, diastolic, and pulse pressures invariably fell. After 8 to 10 beats the blood pressure started to rise to its original level.

Squat-lying caused only minimal changes in blood pressure and pulse rate. A graph of the beat-by-beat changes in one subject when he squatted from the standing and lying positions is shown in Fig. 2; the steady-state values are shown in Table II.

The effects of squatting in water are shown in Fig. 1,*B* and Table III. The bradycardia and rise in blood pressure after squatting in air were virtually abolished in water.

The values for cardiac output and "central blood volume" of the 2 normal subjects during squatting are shown in Table IV. Squatting increased both parameters in both subjects.

All 3 patients with atrial septal defect had minimal changes in blood pressure and pulse rate when they squatted from the standing position. A continuous tracing from one of these subjects is shown in Fig. 3. The tracings from the other 2 were similar.

A continuous tracing of arterial pressure and oxygen saturation in Patient 3 with Fallot's tetralogy is shown in Fig. 4. This boy, who had a history of squatting, had the lowest arterial oxygen saturation of all the patients studied, and felt faint if he stood up for more than a minute. His pulse rate increased from 120 to 168 per

Table V. Blood pressure, pulse rate, and oxygen saturation in 7 patients with Fallot's tetralogy studied at rest

Patient	B.P.	Standing		Squatting				
		Pulse	Saturation	B.P.	Pulse	Saturation	Immediate fall in saturation	A.T.* (sec.)
1.		156	66		126	80	+	8
2.	130/65	114	81	160/90	96	88	+	10
3.	105/50	168	49	125/65	120	65	+	30
4.	93/40	105	77	114/51	94	86	+	9
5.	98/66	136	85	114/79	104	90	+	12
6.	92/60	90		115/70	80			
7	125/60	138	74	150/65	108	81	+	6
Mean	107/57	130	72	130/70	104	82		

*Appearance time of rise in saturation

Table VI. Changes in arterial oxygen saturation after exercise in 7 patients with Fallot's tetralogy

Patient	Saturation after exercise	Improvement in saturation on squatting	Bradycardia on squatting (beats/min.)	Immediate fall in saturation	A.T.* (sec.)
8.	50	−	6	+	
9.	71	+	12	+	10
10.	65	+	24	−	5
11	83	+	18	−	5
12.	81	+	31	+	8
13	75	−	0	+	
14.	61	+		+	15

*Appearance time of rise in saturation.

Table II. *Blood pressure and pulse rate of 8 normal subjects in different postures*

Subject	*Age (yr.)*	*Sex*	*Standing*		*Squatting*		*Lying*		*Squat-lying*	
			B.P	*Pulse*	*B.P.*	*Pulse*	*B.P.*	*Pulse*	*B.P.*	*Pulse*
N. T.	12	F	140/62	120	145/90	108	136/80	96	135/82	90
M. M.	22	M	110/55	102	135/60	72				
D. C.	30	M	130/80	120	150/90	96				
W. K.	32	M	135/65	96	150/75	90				
T. F.	33	M	110/55	84	125/60	72				
T. O.	33	M	150/95	96	185/120	72	150/90	66	160/100	60
M. M.	38	M	130/85	96	160/90	70	128/70	63	128/70	60
C. W.	41	M	140/60	90	160/65	68	145/55	70	145/60	70
Mean			130/70	101	151/81	79				

Table III. *Blood pressure and pulse rate in normal subjects during squatting in and out of water*

Subject	*Age (yr.)*	*In air*				*In water*			
		Standing		*Squatting*		*Standing*		*Squatting*	
		B.P.	*Pulse*	*B.P.*	*Pulse*	*B.P.*	*Pulse*	*B.P.*	*Pulse*
B. D.	20	120/90	88	135/95	74	130/95	75	135/90	75
L. T.	30	120/80	100	135/100	88	120/80	88	120/80	88
T. O.	33	130/90	90	140/100	74	140/100	78	140/100	78
R. L.	31	120/90	84	130/90	72	140/100	78	140/100	78

Table IV. *Cardiac output and "central blood volume" measured by dye-dilution method in 2 normal subjects in the standing and squatting positions*

Subject	*Standing*		*Squatting*	
	Cardiac output (L./min.)	*"Central blood volume" (L.)*	*Cardiac output (L./min.)*	*"Central blood volume" (L.)*
T. O.	5.9	1.6	9.2	1.9
	5.5	1.4	8.7	2.3
M. M.	6.7	2.3	13.4	3.2
	6.9	2.3	9.9	2.6
Mean	6.3	1.9	10.3	2.5

steady-state measurements of blood pressure were all higher in the squatting than in the standing position, but were always less than the values obtained immediately after squatting. There was always a bradycardia soon after squatting, and ear oximetry showed no change in saturation in any subject. When the subjects stood up,

in saturation on squatting (5 seconds) was seen in Patients 10 and 11. The oximetric tracing from Patient 11 is shown in Fig. 5. This tracing also shows that in this patient the first change after squatting was a rise in saturation. Squatting caused an immediate fall in saturation in all except Patients 10 and 11; this fall preceded the rise in saturation by about 4 seconds. An oximetric tracing from Patient 12 which reveals the initial fall in saturation is shown in Fig. 5. A similar fall in saturation, not followed by a rise, was seen in oximetric tracings from some patients with atrial

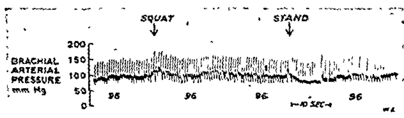


Fig. 3. Arterial pressure tracing in a patient with atrial septal defect, showing minimal changes in blood pressure and pulse rate caused by squatting

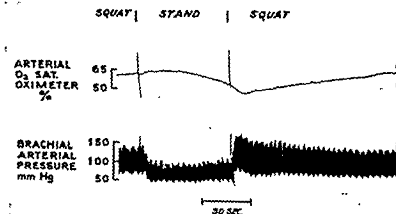


Fig. 4. Changes in arterial oxygen saturation and blood pressure on standing and squatting, in Patient 3 with tetralogy of Fallot.

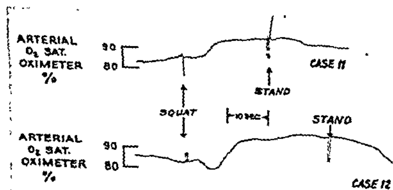


Fig. 5. Oximetric tracings of arterial oxygen saturation in 2 patients with Fallot's tetralogy show timing of changes in saturation after squatting.

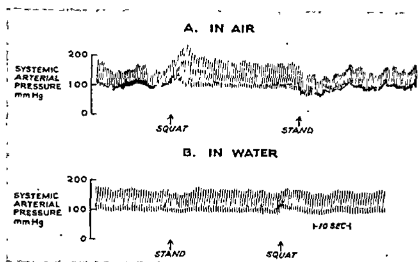


Fig. 1. Changes in arterial pressure of a normal subject when squatting and standing, in air and immersed in water up to heart level.

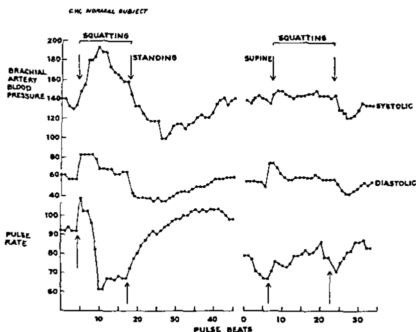


Fig. 2. Graph of the changes in blood pressure and pulse rate, beat by beat, of a normal subject when squatting from the standing and supine postures.

minute when he stood, and his oxygen saturation fell below 50 per cent. Continuous tracings of arterial pressure were obtained in 5 other patients with Fallot's tetralogy, and steady-state measurements of blood pressure, pulse rate, and oxygen saturation are shown in Table V. The average increase in arterial oxygen saturation caused by squatting was 10 per cent, and the increase in blood pressure and decrease in pulse rate were comparable to those in the normal subjects, although the patients with Fallot's tetralogy usually had a lower blood pressure and faster pulse rate initially than did the normal subjects.

The effects of squatting during recovery from exercise are shown in Table VI. Two of these 7 patients had no change in saturation when they squatted and stood after exercise. The shortest appearance time of a rise

This patient was unable to stand for more than a minute or two without feeling faint and was equally relieved by squatting and by lying down. He probably resembles the patients seen by Taussig before operation was available for the relief of this lesion.

We can only deduce the exact sequence of events after squatting from the changes in saturation measured with ear oximetry. The first change was usually a brief fall in saturation that was followed by a prolonged rise. We think that squatting increases venous return and shifts blood from the legs to the heart and lungs. In this process, some extra blood may be shunted into the aorta to account for the initial fall in saturation. The immediate rise in peripheral resistance postulated by Sharpey-Schafer would minimize this early fall in saturation, and we presume that this factor was responsible for the lack of an initial fall in saturation in Patients 10 and 11.

We postulate that squatting increases left ventricular output by increasing the volume of blood in the central reservoir in the lungs. This hypothesis is supported by the increased "central blood volume" in normal subjects in the squatting position. It is also consistent with the fact that our patients with large left-to-right shunts, who presumably had an increased amount of blood in the lungs, had no change in blood pressure when they squatted. We think that in these patients the increased venous return makes little difference to the already large volume of blood available to fill the left ventricle.

We agree with Taussig's impression that squatting can be expected to increase the arterial saturation of patients with a small pulmonary blood flow. Presumably, patients with increased pulmonary blood flow resemble our patients with atrial septal defect in showing *no* change in blood pressure on squatting, and, therefore, no increase in left ventricular output or decrease in shunt.

By no means all patients with a small pulmonary blood flow and a low arterial oxygen saturation derive benefit from squatting, and it seems probable that the anatomy of the heart in Fallot's tetralogy accounts for the frequent and marked improvement in saturation when patients with this lesion squat. The hypothetical explanation we propose is based on the belief that the shunt in Fallot's tetralogy is usually from the right ventricle to the aorta. This belief is supported by the fact that a catheter rarely passes through a ventricular septal defect into the left ventricle of patients with this condition, but it often passes into the aorta. If the shunt is from the right ventricle to the aorta, a left ventricular output of fully saturated blood mixes at the root of the aorta with desaturated mixed venous blood from the right ventricle, some going to the lungs and some to the aorta. In these circumstances, small changes in the parallel resistances to flow to the lungs and periphery or small changes in the output of either ventricle would produce marked changes in arterial saturation. Indirect evidence that this happens is given by the marked respiratory fluctuations in arterial oxygen saturation in patients with Fallot's tetralogy.[13] Inspiration presumably increases right ventricular output and causes more blood to shunt from right to left.

If this hypothesis is correct, improvement in saturation caused by squatting should be less marked if the circumstances which cause this delicately balanced shunt are absent. We would postulate that this is the case in pulmonary stenosis with an atrial septal defect, atrioventricular canal, low muscular ventricular septal defect, or single ventricle, wherein the blood shunted from the right side should be thoroughly mixed with the blood returning from the lungs We have not studied proved cases of all these lesions, but squatting does not usually increase the saturation in patients who have pulmonary stenosis with atrial septal defect. Another set of lesions in which the delicately balanced shunting should not occur are those in which blood is distributed to the lungs from the aorta (truncus arteriosus, pulmonary atresia, and Fallot's tetralogy with patent ductus arteriosus). Here the blood from the two sides of the heart should mix in the aorta before being distributed to the lungs and periphery. We have studied 3 patients with pulmonary atresia and 1 with truncus arteriosus, and in none of them did squatting increase the arterial saturation after exercise. Further support for our hypothesis

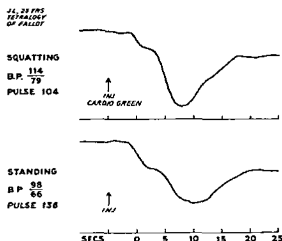


Fig. *6*. Dye-dilution curves from Patient 5 with Fallot's tetralogy, in the squatting and standing postures, showing decrease in right-to-left shunt on squatting

septal defect, pulmonary stenosis with reversed interatrial shunt, or tricuspid atresia.

The results in Patients 4 and 14, who also squatted in the lying position, were similar to those obtained by Brotmacher.[7] In Patient 4 the arterial saturation fell 2 per cent, and in Patient 14 it rose 3 per cent. There were insignificant changes in pulse rate and blood pressure. In Patients 4 and 7, dye-dilution curves in the lying and squat-lying positions were similar, showing no change in the volume of blood shunted from right to left. In Patients 5 and 6, dye-dilution curves were recorded in the squatting and standing positions. Fig. 6 shows the curves of Patient 5; those of Patient 6 were similar. The first peak of the dye curve was smaller in the squatting position, indicating a decrease in the right-to-left shunt. This finding was confirmed in Patient 4 by measurements of systemic arterial and right atrial oxygen content in the squatting and standing positions. If a pulmonary venous oxygen saturation of 97 per cent is assumed, it can be calculated that squatting decreased the systemic oxygen A-V difference from 112 to 103 ml. per liter, whereas it decreased the effective pulmonary A-V oxygen difference from 162 to 128 ml. per liter. If the oxygen uptake did not change with posture, these results indicate a decrease in the right-to-left shunt.

Discussion

Our results in normal subjects confirm the findings of Sharpey-Schafer and show that squatting increases blood pressure and causes a secondary bradycardia. His suggestion that squatting increases the cardiac output has been shown to be correct, and there is also an increase in "central blood volume." Our findings confirm Brotmacher's conclusion that squat-lying has little or no effect on the circulation and suggest that gravity plays a dominant role in the circulatory changes produced by squatting. This conclusion is further borne out by the studies in water, from which we conclude that kinking of the arteries or veins to the legs cannot be important. Squatting is therefore comparable to lying down and affects the circulation almost entirely by removing the force of gravity on the circulation below heart level.

Only 6 of the 14 patients studied gave a history of having squatted of their own accord, and there was no difference between the results in these habitual squatters and the results in the patients who had not learned to squat to relieve their symptoms. There was also no difference between the results in patients with infundibular stenosis and the results in patients with valvular stenosis. We confirmed the finding that squatting increases arterial oxygen saturation,[11,12] and the proportion of our patients who showed a rise (86 per cent) is similar to that reported by others.[2] If oxygen consumption does not change, the rise in systemic output caused by squatting must result in an increase in mixed venous oxygen saturation after a time lag of one circulation. In some of our patients the arterial oxygen saturation rose sufficiently soon after squatting to rule out changes in mixed venous oxygen saturation as the only mechanism. The alternative explanation of a reduction in the volume of blood shunted from right to left is supported by the difference in the dye-dilution curves obtained when the patients were in the squatting and standing positions.

We presume that the increase in arterial oxygen saturation is responsible for the symptomatic relief. However, the results in Patient 3 suggest that relief of faintness may also be important in severe cases.

Extrasystoles and parasystole

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Early attempts to explain the origin of extrasystoles with fixed coupling by a parasystolic mechanism failed. In a true ventricular parasystolic rhythm, independent from the basic rhythm, continuous variations in the length of the coupling must be expected. In atrial parasystole, variations of the coupling often are of a minor degree, since the parasystolic impulse is conducted to the sinus node and discharges it; thus, both rhythms are linked. On the other hand, with true extrasystoles the coupling is constant; the variations are no more than a few hundredths of a second. Therefore, the principal sign for differentiation of parasystole from extrasystoles is the fixed coupling of the latter.

It is ironic that Kaufmann and Rothberger, who originated the modern concept of parasystole, described arrhythmias that today cannot be accepted as representatives of parasystole. Only parasystoles with "simple interference," demonstrated first by Singer and Winterberg,[12] are now considered to be true parasystoles.

Recently, a form of parasystole has been described in which impulses are fired rapidly.[9] In such cases it is not necessary to assume the presence of a protection block of the parasystolic center. The very speed of the firing will protect the center and prevent its depolarization by other conducted impulses.

The center fires impulses rapidly, and only every second or third impulse is answered by the ventricles. If there were a full response, the pattern would be identical to that of a ventricular tachycardia, and it is possible that some forms of parasystole represent a ventricular tachycardia with exit block.

Parasystoles can be produced experimentally. They are seen in the dog heart after injection of barium chloride and quinidine when the heart is stimulated electrically,[7] and also appear after focal application of veratrine.[11] In all these experimental parasystoles the rate of the ectopic center is fast.

The present study was undertaken in order to investigate the relationship between experimental ventricular tachycardia and parasystole, and to examine the behavior of the coupling in parasystole caused by a rapidly firing center.

Method

The dogs used in the experiments weighed between 10 and 15 kilograms. The anesthesia consisted of Nembutal (18 mg./Kg.) and morphine (8 mg./Kg.) administered intraperitoneally. After artificial respiration was instituted, the sternum was re-

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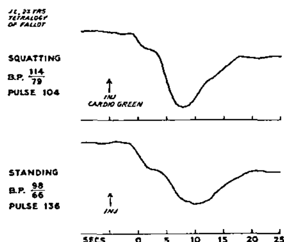


Fig. 6. Dye-dilution curves from Patient 5 with Fallot's tetralogy, in the squatting and standing postures, showing decrease in right-to-left shunt on squatting.

septal defect, pulmonary stenosis with reversed interatrial shunt, or tricuspid atresia.

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and 73, but 12 out of the 16 seen in Fig. 1 are 70 or 71. This represents two interectopic intervals.

In Fig. 1,*A-C*, 16 couplings (distance between sinus beat and following ectopic beats) are seen. They had lengths of 42, 43, 42, 41, 43, 42, 40, 42, 42, 41, 41, 40, 41, 43, 42, and 39. Therefore, they varied only between 39 and 43, that is, by 0.04 second, which is within the limits of the variations of the couplings seen in extrasystoles and called "constant."

Fig. 1,*D* was obtained from another experiment, also after application of sodium chloride. The successive intervals measure 29, 26, 32, 30, 29, 25, 32, 30, 30, 24, 32, 29, 30, 27, 32, 29, 29, 26, 32, 31, 29, 30, 26, 33, 29, 21, 29, and 31. In this tracing the coupling varies only between 32 and 33, the ectopic interval between 29 and 30, and the interval between two ectopic beats separated by a sinus beat is 56 to 59. In this experiment, therefore, a parasystole exists with constant distance between sinus beats and the first ectopic beat of a series.

Fig. 2, also obtained after application of sodium chloride, shows longer intervals between the ectopic beats interrupted by sinus beats. The strips are continuous but have been divided into three parts for the purpose of illustration. The arrhythmia was registered after a prolonged ectopic tachycardia had subsided. The successive intervals between the ectopic beats measure 37, 37, 37, 37, 37, 37, 75, 37, 37, 39, 37, 37, 75, 37, 37, 38, 40, 38, 38, 77, 38, 36, 39, 40, 38, 40, 38, 154 (38.5 × 4), 39, 39, 38, 40, 39, 39, 38, 39, 190 (38 × 5), 38, 41, 39, 40, 39, 39, 39, 39, 40, 39, 38, 38, 38, 38, 269 (38.5 × 7), 39, and 40.

The ectopic intervals vary between 36 and 40. The long intervals with sinus beats in between are exact multiples of the shortest interectopic intervals. Combination beats are seen in several places. On 5 occasions the distances between a sinus beat and an ectopic beat (coupling) can be seen; these measure 38, 38, 39, 40, and 40.

Fig. 3 was obtained after focal application of sodium oxalate. Series of ectopic beats are interrupted by one sinus beat.

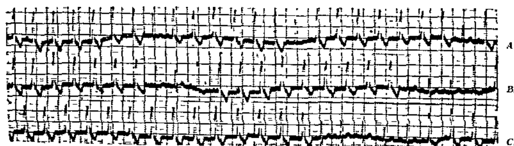


Fig. 2 Parasystole which shows longer series of sinus beats after subepicardial injection of sodium chloride. The long intervals filled by sinus beats are a multiple of an ectopic period. The distances between sinus and ectopic beats (couplings) show little variation. The three strips are continuous.

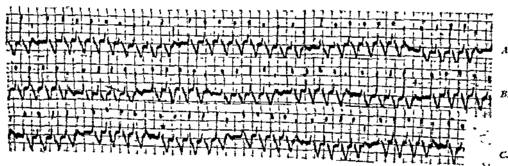


Fig 3 Application of sodium oxalate provokes a parasystole with constant coupling and little variation of rate (continuous tracing).

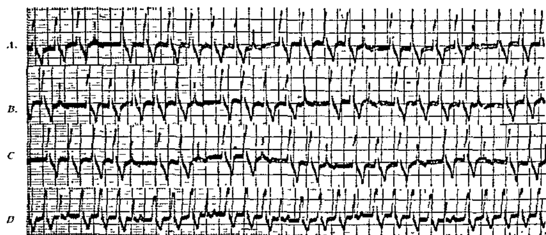


Fig. 1. Parasystole after focal application of a hypertonic solution of sodium chloride on the right ventricle (*A-C*). The top three tracings are parts of a continuous strip. *D* shows a parasystole with a fixed coupling from another experiment after application of sodium chloride.

moved and the pericardium opened. The vagi were severed in the neck. The electrocardiogram was registered in Lead II. By means of a tuberculin syringe, 0.05 c.c. of a 30 per cent solution of sodium chloride or a 3.8 per cent solution of sodium oxalate or citrate was injected subepicardially, usually on the right ventricle and in an area devoid of major blood vessels. These substances have been shown in previous studies[8] to elicit paroxysmal ventricular tachycardias.

Results

A parasystolic arrhythmia appeared in 38 per cent of the experiments with sodium chloride and in 12 per cent of the experiments in which sodium oxalate or citrate had been used. In all experiments a ventricular tachycardia was observed at first, followed after a variable time by interruption of the ectopic beats by one or more sinus beats. This arrhythmia lasted long enough to prove the presence of a parasystolic center in the ventricle which was undisturbed by the sinus beats. Whenever the vagus was stimulated during this phase and the sinus rhythm was inhibited, the ventricles responded to all impulses of the parasystolic center, and this led to a ventricular tachycardia. This feature is totally different from the response seen with coupled extrasystoles; when the basic rhythm is interrupted, these coupled beats also vanish, since they are dependent on the former. Occasionally, a ventricular tachycardia, i.e., an uninterrupted series of ectopic beats, appeared spontaneously. In some of the experiments this switch from parasystole to tachycardia came several times. When the ectopic ventricular beats were conducted in reverse to the atria, the chain of ectopic beats lasted longer, sometimes up to 4 minutes. When there was no reverse conduction, the sinus beats could reach the ventricles earlier and a parasystole appeared as soon as the ectopic beats slowed down.

Fig. 1 shows a typical parasystole obtained after focal application of sodium chloride on the right ventricle. The tracing was registered after the disappearance of a long run of ventricular tachycardia. For the purpose of illustration, the strip has been divided into three parts (Fig. 1,*A-C*). A series of 2 to 6 ectopic beats is interrupted by one sinus beat. The intervals between the ectopic beats in Fig. 1 measure (in hundredths of a second) 37, 35, 71, 36, 38, 35, 35, 35, 73, 34, 35, 35, 71, 34, 36, 35, 70, 35, 36, 34, 71, 36, 36, 34, 35, 71, 34, 36, 34, 70, 33, 71, 35, 35, 34, 71, 34, 71, 35, 36, 34, 70, 34, 69, 34, 69, 34, 71, 36, 35, 73, 34, 70, and 35. Thus, the variation between the ectopic beats is only 5 (between 33 and 38), and 27 of the 39 intervals are between 34 and 35. The intervals between two ectopic beats separated by a sinus beat measure between 69

means of artificial respiration.[10] The ectopic beats had stopped because of the effect of hypercapnia, but reappeared when the area to which veratrine had been applied was warmed. The intervals between the ectopic beats in Fig. 5,*A* are 26, 26, 27, 152 (25 × 6), 26, 26, 29, 152, 27, 26, 25, 52, 26, 26, 150, 23, 26, 25, 22, 22, 24, 23, 24, 20, and 47. In Fig. 5,*B* the successive interectopic intervals measure 24, 24, 23, 26, 23, 23, 23, 51, 126, 27, 23, 21, 25, 161, 25, 26, 26, 48, 25, 28, 156, 26, 24, 26, and 51.

The couplings measure 28, 26, 28, 28, 25, 26, 30, and 28. The presence of an exit block is demonstrated by the fact that the pauses are multiples of an interectopic interval. The long intervals between the ectopic beats separated by a sinus beat are multiples of the ectopic period. Thus, a parasystolic mechanism must be considered.

Discussion

An important finding in the present experiments is the comparative ease with which it was possible to create a parasystole in the dog with a variety of substances. This arrhythmia appeared more frequently after the application of a hypertonic solution of sodium chloride but was indistinguishable from that provoked by sodium oxalate or sodium citrate, substances which presumably lead to rhythmic impulse formation because they remove calcium from the cells. It seems that only two conditions are necessary for the experimental creation of a parasystolic arrhythmia, namely, a long chain of ectopic beats and the prevention of reversed conduction of these beats to the atria. Even when no sinus beat interrupted the ectopic chain, it could be demonstrated that the ectopic center was protected from other impulses Its rhythm was maintained in spite of interruptions by ectopic beats created by mechanical stimulation of the other ventricle.

It is now proved that protection of the ectopic center was present in the ectopic chains caused by barium chloride and mechanical or electrical stimulation,[7] aconitine and stimulation,[7] veratrine,[11] sodium chloride, oxalate, and citrate applied locally (the present report). The appearance of parasystole through the use of such different substances seems to indicate that the protection of the center is due to the rapidity of the impulse formation rather than to a hypothetical block surrounding the area. Ventricular parasystole would be seen in ventricular tachycardia with exit block, and block preventing all ventricular ectopic beats from being conducted back to the atria and thus allowing the impulses from the sinus node to reach the ventricles. It is interesting to note that ventricular parasystole, like ventricular tachycardia, usually appears in patients with pre-existing heart disease.

This theory does not rule out other mechanisms of parasystole. In surviving strands of specialized tissue, Wachstein[12] observed independent rhythmic activity of several centers simultaneously.

In the experiments described in this presentation the periods without extrasystoles are multiples of the prevailing ectopic period. The calculated ectopic periods in the pauses filled with sinus beats are occasionally slightly shorter than the ectopic periods which could be measured directly. This is a well-known phenomenon, seen clinically, but not fully explained. The fact that the interectopic periods separated by sinus beats are a multiple of the ectopic period is particularly important if the coupling shows variations. If the coupling is fixed, it is readily found that the pause between ectopic beats is a multiple of one of several cycle lengths[6] even in the absence of parasystole.

A study of the literature shows that in some instances of ventricular tachycardia a parasystole of the type shown in the present paper occurred. For example, Figure 189 in Wenckebach and Winterberg's book shows this phenomenon[13]; Holzmann[2] described a paroxysmal ventricular tachycardia in a 55-year-old patient in which, occasionally, sinus beats would reach the ventricle and give a picture of interference dissociation; the distances between the last ectopic beat before, and the first ectopic beat after the sinus beat are a multiple of the ectopic period. The same type of tracing is seen in Figure 468B in Massie and Walsh's book.[3]

The possibility of eliciting parasystole experimentally also provided an oppor-

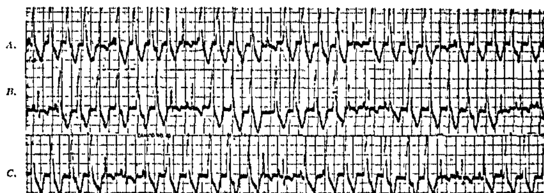


Fig. 4. Focal application of sodium citrate creates a parasystole with greater variations of the duration of the coupling because of greater differences between the rates of the sinus rhythm and the ectopic rhythm (continuous tracing).

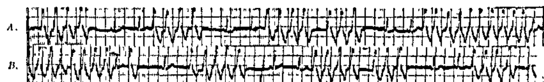


Fig. 5. Focal application of veratrine had caused a ventricular tachycardia which disappeared after the dog inhaled a mixture of 20 per cent carbon dioxide and 80 per cent oxygen. Warming of the area on which veratrine had been applied provoked a parasystole with exit block. The two strips show the effect of two attempts of warming.

A typical parasystole is present; there is only slight variation of the intervals, which measure 31, 62, 31, 32, 32, 32, 32, 32, 32, 32, 62, 32, 32, 32, 33, 31, 32, 32, 64, 32, 32, 32, 32, 32, 61, 34, 31, 30, 62, 32, 32, 30, 32, 63, 32, 31, 33, 63, 31, 32, 32, 62, 32, 31, 33, 62, 32, 30, 32, 62, 32, 30, 30, 63, 30, 30, 32, 31, 59, 30, 33, 32, 60, 32, 32, 31, 60, 33, 32, 31, 33, 61, 32, 31, 30, 60, 32, 32, 30, 62, 30, 30, 29, and 60. The ordinary interectopic intervals vary only between 29 and 34, and the periods including a sinus beat are equal to two ectopic periods. The distances between sinus beats and the next ectopic beat (the coupling) measure 36, 34, 37, 36, 37, 36, 36, 36, 36, 35, 36, 31, 34, 33, 33, 33, 34, and 31; they vary between 31 and 37.

Fig. 4 was registered after application of sodium citrate. One to two sinus beats are seen between the ectopic beats after the continuous tachycardia has subsided. There are many combination beats. The P waves of the sinus beats are often clearly visible in the ectopic beats, making obvious the presence of the two rhythms, the sinus rhythm and the ectopic ventricular rhythm. The distance between the sinus beats is 48, which represents a rate of 125 per minute. The ectopic periods measure 34, 37, 37, 70, 35, 36, 36, 69, 35, 36, 36, 71, 37, 37, 36, 73, 37, 37, 37, 74, 37, 39, 40, 40, 118 (39.5 × 3), 39, 41, 41, 42, 41, 116, 41, 37, 56, 54, 40, 36, 39, 42, 40, 119, 40, 40, 41, 41, 120, 42, 44, 45, 40, 40, 44, 120, 44, 41, 43, 40, 48, 40, 126, 46, 42, 40, and 45.

This tracing is interesting because of the gradual increase in the duration of the interectopic interval which is associated with a corresponding prolongation of the interval between two ectopic beats separated by a sinus beat. In the middle of Fig. 4,*B* are two unusually long interectopic intervals which we cannot explain. The couplings in Fig. 4 measure 37, 36, 36, 38, 39, 40, 37, 43, 40, 42, 45, and 44. The variations between 36 and 44 are considerable and are not seen in the majority of clinical cases of extrasystoles with fixed coupling.

Fig. 5,*A* was obtained after focal application of veratrine and while a mixture of 20 per cent carbon dioxide with 80 per cent oxygen was being administered by

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tunity for study of the coupling, which is the distance between the sinus beat and the first ectopic beat of a series. The experiments reveal that when there was a rapid sinus and a rapid ectopic rate, the relationship between the sinus beat and the ectopic beat was constant, an almost fixed coupling was present (Figs. 1-3). When there was a greater difference in rate between the two rhythms, the coupling varied (Fig. 4).

These experiments show that it is possible to obtain extrasystoles with constant or almost constant coupling under certain conditions, as a consequence of a parasystolic impulse formation. This will also be the case when the parasystolic center fires impulses which are subthreshold and which can only elicit a response after an impulse spreads over the heart. This is similar to the classic experiment of Wedensky on the nerve-muscle preparation. When the nerve was stimulated by infrathreshold faradic stimuli, the muscle failed to respond; when one strong induction shock was applied to the nerve, leading to a muscular contraction, the previously subthreshold impulses were then able to elicit a response.[14] The same phenomenon could be observed when crystals of sodium chloride, instead of the faradic stimulation, were applied to the nerve.[4] The infrathreshold impulses formed in the area on which sodium chloride had been applied became threshold in the wake of a conducted impulse after application of one induction shock. Finally, on the strips of specialized fibers of the dog heart (called *Purkinje fibers*) it was also observed that weak, infrathreshold condenser discharges elicited a response only after a strong electrical stimulus had excited the strip.[1] This change of excitability after a conducted impulse is not caused by the supernormal phase only, because it may occur as late as 0.5 second after a conducted impulse.[5] The variation of the coupling will be small in the presence of this phenomenon, not only because the rates of the two centers are rapid, but also because the heart muscle can only respond during a certain phase of diastole.

It is possible that some extrasystoles, such as those seen in myocardial infarction, are elicited by a parasystolic mechanism in the manner just discussed. In these cases an electrotonus caused by the injury current may lead to the formation of rapid, weak impulses which, in the favorable case, will lead to only one extracontraction after a conducted sinus beat. The coupling will be fixed if this parasystolic center forms rapid impulses.

Summary

Ventricular ectopic tachycardias were created by the focal injection of 0.05 c.c. of a 30 per cent solution of sodium chloride, or a 3.8 per cent solution of sodium citrate or oxalate into the subepicardial layers of the ventricular myocardium. These tachycardias were often followed by a parasystolic rhythm.

The experiments show that a rapidly firing center is protected from the normal impulses which spread over the heart, and, thus, the hypothesis of entrance (protection) block is not necessary.

These parasystoles provide an opportunity for study of the distance between ectopic beats and preceding normal beats (coupling). It was found that this distance varies little if normal and ectopic rhythms are rapid and have an almost equal rate.

Marked variations in the coupling occur if the rates differ. Little variation in the coupling may occur if the impulses of a rapid parasystolic center become effective only shortly after a conducted beat.

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Fig. 1. Internal defibrillator calibration graph.

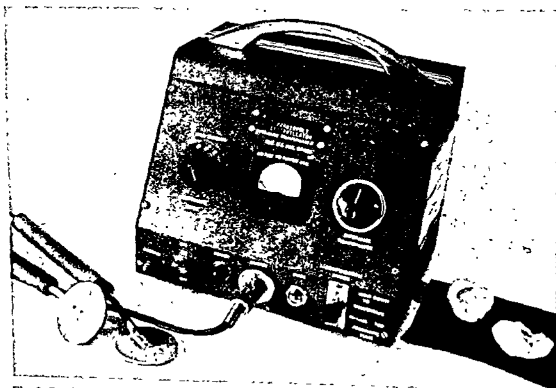


Fig. 2. Cardiovolt internal defibrillator with semi-automatic spring-operated impedance-compensator switch.

Impedance-compensated defibrillator

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Effective defibrillation of the ventricles of the heart by electrical countershock requires an optimum value of electrical energy. The heart impedances of 25 mongrel dogs were measured by using a modified Wheatstone bridge, the alternating-current signal of which was small enough to prevent fibrillation, yet large enough to produce a null-sound in the headphones after being amplified.

Optimum values of electrical countershock were determined by initially fibrillating the ventricles in the dog's open chest with a 10-volt electrical shock for 1.0 second. Then, the alternating-current defibrillating voltage was increased by small discrete values until effective defibrillation was observed. It was found that the heart appeared to obey the empirical law (Fig. 1):

$$E_{int.} = 1.8\,Z + 5$$

where $E_{int.}$ = internal defibrillating voltage, and Z = heart impedance in ohms. For example, a 50-ohm heart required 95 volts of alternating current for 0.1 second to effectively defibrillate the ventricles without causing visible myocardial burns.

An *impedance-compensated defibrillator* (Fig. 2) was then designed with a dual control for concurrent Wheatstone bridge balance and for optimum value of electrical countershock adjustment, in accordance with the above law. Headphones were later replaced by a rectifier-type microammeter (0-50 microamperes) to provide for visual observation of Wheatstone bridge balance (Fig. 3).

The principle of impedance-compensation, which provides for essentially constant current through the heart for any heart impedance, was then employed by defibrillating the ventricles through the closed chests of 11 mongrel dogs. Unequal diameters of chest electrodes were used; the smaller electrode was strapped to the left side of the chest, and the larger one was strapped to the right side of the chest. The heart was then externally fibrillated by using 225 volts of alternating current for 0.4 second. Ventricular fibrillation was confirmed not only by observing zero blood pressure by means of a cannulated sphygmomanometer, but also by means of a direct-writing electrocardiograph. Chest impedance was measured by the modified Wheatstone bridge method. The heart was then externally defibrillated by delivering an electrical countershock of

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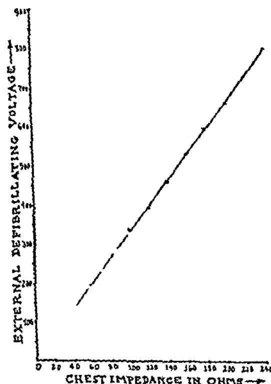


Fig. 4. External defibrillator calibration graph.

0.25-second duration in accordance with the following empirical law (Fig. 4):

$$E_{ext} = 3.3\ Z$$

where $E_{ext.}$ = external defibrillating voltage, and Z = chest impedance in ohms. For example, a chest impedance of 200 ohms was observed to require 660 volts of alternating current for 0.25 second to effectively defibrillate the ventricles of the heart. Ten out of 11 dogs survived 3 weeks or longer. A total of 26 recoveries from ventricular fibrillation was achieved with this group of dogs. The only nonsurvivor expired after being subjected to 7 consecutive sequences of fibrillation and defibrillation during the same operation.

Six hand-constructed models of the above-described internal impedance-compensated defibrillator were then assembled and tested for accuracy of calibration in accordance with the afore-mentioned law. These were put into service in 6 different hospital operating rooms located in New York City. All of the models have been functioning successfully, without failure, during the past 5 years. The external defibrillator, however, has not yet been tested on human beings.

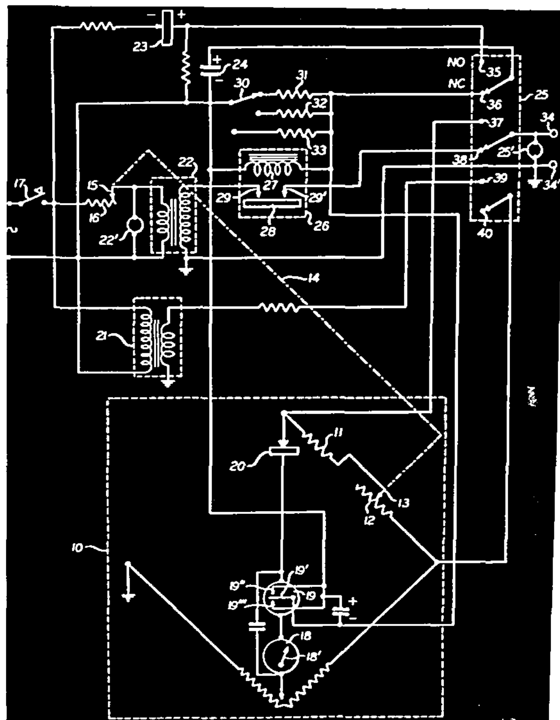


Fig. 3. Schematic diagram of defibrillator. *10:* Wheatstone bridge assembly. *11:* Resistor—47 ohms, 1 watt carbon. *12-13:* Rheostat—wirewound, 50 ohms, 1 watt. *14:* Ganged shaft. *15-16:* Rheostat—16 ohms, 50 watts. *17:* Toggle switch—S P.S T. *18-18':* Microammeter (0-50 microamperes) Simpson Model 127. *19-19'-19"-19''':* Fail—safe microammeter relay. *20:* Germanium diode rectifier—Sylvania 1N54. *21:* Step-down transformer—2.5 volts, center-tapped *22:* Isolation step-up transformer (Stancor model P 6383). *22':* Neon indicator lamp (Ne-51)—red dome. *23:* Selenium half-wave rectifier—100 milliamperes (I.T.T.1004A). *24:* Capacitor—dry electrolytic, 40 mfd, 250 volts. *25:* Spring-operated impedance-compensator switch (triple-pole; double throw). *25':* Neon indicator lamp (Ne-51)—white dome. *26:* Relay—double-break, 2,500 ohms (Potter & Brumfield; MR 1160). *27:* Relay coil—2,500 ohms. *28:* Relay armature. *29-29':* Relay contacts. *30:* Selector switch for timer—wafer type, 3 positions. *31:* Resistor—1,500 ohms, 1 watt carbon. *32:* Resistor—2,000 ohms, 1 watt carbon. *33:* Resistor—3,000 ohms, 1 watt carbon. *34-34':* Heart electrodes. *35-40:* Contacts on impedance-compensator switch.

half the animals it was necessary to stimulate the vagi or to administer vagomimetic drugs in order to expose a latent arrhythmia.

The gas mixtures were prepared volumetrically in a Tissot spirometer and were administered to the animal via a positive pressure respiration pump. The oxygen content of the reservoir gas was determined with the Pauling oxygen analyzer, and checked frequently with the Fry apparatus for gas analysis. In 7 animals, alveolar oxygen concentrations were also measured. In these animals, respiratory rates were recorded, and in 4 animals the minute volume of respiration was estimated.

At the time of operation the limb leads of the electrocardiogram were taken on each animal. During each experiment the femoral arterial pressure and Lead II of the electrocardiogram were recorded. The records were examined for the number of sinus beats, the heart rate (over-all and sinus), and systolic and diastolic pressures. The study periods were about 10 to 20 minutes long, and the last 4 minutes were selected for purposes of comparison.

In order to determine the role of the sinus pacemaker during hypoxia, the chest of one animal with the arrhythmia was opened and, after a test period during which a hypoxic mixture was given, the sinus node was crushed and hypoxia again administered.

The influence of elevation of arterial blood pressure upon ventricular tachycardia was evaluated by means of a Lamson arterial pressure reservoir, used as described by Moe and associates.[6] Two animals were studied in this way at various arterial pressures while they breathed hypoxic mixtures or air.

Results

The method of producing hypoxia outlined above was successful in lowering alveolar oxygen concentrations as shown in Table I. These values are similar to those obtained by Maling and Highman under comparable conditions.[7] A given concentration of oxygen in the inspired gas did not result in the same alveolar oxygen concentration from animal to animal or even in successive applications to the same animal.

Hypoxia was effective in increasing the percentage of sinus beats in all but 2 dogs,

Table I. The effect of various degrees of hypoxia on the concentration of oxygen in alveolar gas (per cent oxygen and pO_2), respiratory rate, and minute volume of respiration

Dog number	Inhaled gas (% oxygen)	Time (min.)	Alveolar gas (% oxygen)	Alveolar gas (mm. Hg)	Respiratory rate per min.	Minute volume of respiration (c.c./min.)
30.	9 7	23	6 1	42 7	64	
32.	Air		14 8	103.6	16	
	10 9	8	5 0	35 0	36	
	Air		14 0	103 6	16	
33.	Air		13 0	91.0	16	
	9 1	17	5 0	35 0	36	
	Air		13 0	91 0	20	
40.	Air		14 0	103 6	24	
	8 5	14	1 0	7 0	24	
	Air		13 5	94 5	24	1,350
	8.5	12	1 0	7 0	32	4,000
	Air		13 5	94 5	12	1,000
43.	Air		13 5	94 5	16	1,375
	5 0		0 0	0.0	28	3,050
49.	Air		13 7	95 9	56	3,000
	6 4	20	1 5	10 5	80	4,700
	Air	10	13 7	95.9	44	2,850
	6.2	20	0 5	3.5	84	6,500
51.	Air		14 0	103.6	36	1,900
	7 4	10	3 0	21.0	66	7,200
	Air	12	14.0	103.6	36	3,200

The effect of hypoxia on experimental ventricular tachycardia

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It has been proposed by Brofman and associates[1] and by Zao and associates[2] that the idioventricular rhythms which occasionally develop after myocardial infarction are generated by the difference in potential between normally perfused and ischemic areas of the heart. These investi[illegible]s have shown that hypoxia abolished the difference in potential between normal myocardial tissue and infarcted areas of heart muscle as indicated by the return of elevated S-T segments to base-line levels during administration of hypoxic gas mixtures to animals with recent infarction. If this "oxygen-gradient theory" is correct, hypoxia should be expected to reduce or abolish ventricular arrhythmias associated with infarction.

This investigation was undertaken to evaluate the effect of hypoxia upon experimental ventricular tachycardia after acute myocardial infarction.

Methods

Twenty mongrel dogs which weighed from 9.5 to 20.0 kilograms were used. The operative technique described by Harris[3] was employed to initiate a stable ventricular tachycardia. Under anesthesia (pentobarbital, 30 mg. per kilogram) and artificial ventilation, the heart was exposed through a 7-cm. incision between the fourth and fifth left ribs. The pericardium was opened to expose the anterior descending branch of the left coronary artery. A 16 or 18 gauge needle was laid parallel to the artery, and one ligature was snugly tied around both artery and needle. The needle was then removed. One half hour later a second ligature was tied tightly to occlude the artery completely. The pericardium and chest wall were sutured; care was exerted to express the residual air from the thorax and also to inflate the lungs fully after closure.

On the day after the operation, when ventricular tachycardia had appeared, the dogs were prepared for electrocardiographic and arterial pressure recordings during exposure to various hypoxic gas mixtures which contained from 0 to 16.4 per cent oxygen. The anesthesia necessitated by these procedures commonly caused a reversion to sinus rhythm,[4,5] and in about

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supraventricular origin) was diminished by hypoxia in 8 of the 14 experiments listed in the table, was accelerated slightly in 3, and was essentially unchanged in 3. The percentage of supraventricular beats, however, was significantly increased by hypoxia in 12 of the experiments, including those in which the over-all frequency diminished. In each case the beats of sinus origin were now sufficiently numerous to permit measurement of the S-A nodal frequency. Had the accession of the supraventricular pacemaker been due solely to acceleration of the S-A node, then clearly the over-all heart rate should have increased in each case. Therefore, the frequency of the ventricular focus (foci) must have diminished under the influence of hypoxia. Thus, for example, in Dog No. 67 the ventricular focus was firing at a rate of 173 per minute at a time when less than one fifth of the beats seen on the electrocardiogram were of sinus origin. When hypoxia was administered, the arrhythmia terminated and all beats seen were of sinus origin at a frequency of 138 beats per minute. Upon exposure to air, ventricular tachycardia returned at a rate of 195 per minute. Slowing of the ventricular focus must have occurred during hypoxia before conversion to sinus rhythm could take place.

That a more rapid sinus rate was *capable* of capturing the cardiac rhythm was evident, for in many experiments the ventricular tachycardia was initially completely obscured by the supraventricular pacemaker, and was exposed only after the administration of vagomimetic drugs.

Another experiment designed to study the possible significance of the rates is shown in Table III, which illustrates the effect of destruction of the S-A node. Again, hypoxia (8.3 per cent oxygen) converted ventricular tachycardia to sinus rhythm at a slower rate, and resumption of air-breathing restored the ventricular pacemaker. After destruction of the sinus node the A-V node became the pacemaker for the few beats of supraventricular origin seen on the electrocardiogram. Another exposure to hypoxia terminated the ventricular tachycardia, and an A-V nodal rhythm at a rate slower than either the sinus rate or the previous ventricular rate was present.

*Table II. The effect of hypoxia on the over-all rate and sinus rate (ventricular complexes of supraventricular origin)**

Dog number	Control		Hypoxia		Posthypoxic control	
	Over-all rate	Sinus rate	Over-all rate	Sinus rate	Over-all rate	Sinus rate
22	176		132	135	160	150
25.	173		119	110	161	
27.	144		144	130	135	
30.	195		175	180	175	
31.	150		140	140	160	150
32	165		170	180	190	190
33	144		154	154	140	140
39.	120		83	83	97	
40.	154		112	115	171	140
43.	179		153	160		
49	176		174		186	
51.	181	180	178	175	198	195
67.	173		138	138	195	
78	144		150	150	191	
Mean	162 4		144 4	142 3	166 0	160 8
S D.	19 7		26 2			

*During control periods, "sinus" beats were so few in number that the frequency of the S-A node could not be measured, except in Dog No. 51.

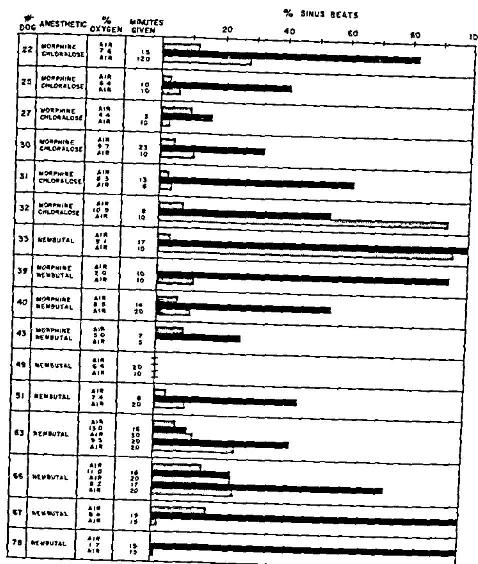


Fig. 1. Comparison of the effects of hypoxic gas mixtures on the percentage of sinus beats in 16 dogs. Stippled bars represent control values, black bars represent values recorded during last 4 minutes of hypoxia.

as is evident from Fig. 1. The effective range of hypoxia appeared to be in concentrations below 10 per cent oxygen. The mean percentage of sinus beats in the records obtained prior to treatment was 5.8 per cent, with a standard deviation of 4.9 per cent, whereas the mean for the group during exposure to gases which contained less than 10 per cent oxygen was 58 per cent, with a standard deviation of 32 per cent. A difference of this magnitude is highly significant ($p = <0.001$). With an oxygen concentration of less than 5 per cent, sudden death from fibrillation became likely. Shortly after restoration of air, the percentage of sinus beats dropped to values not significantly higher than those recorded before hypoxia.

Inasmuch as the sinus rate is often increased during hypoxia in normal animals, it might be thought that the accelerated sinus rate could overtake a ventricular focus and assume the pacemaker role. In most of the experiments, ventricular complexes of supraventricular origin occurred singly during exposure to air, so that the "control" frequency of the S-A nodal pacemaker could not be determined (see Table II). However, the over-all ventricular rate (including the complexes of

blood pressure was prevented by the pressure regulator, 6.1 per cent oxygen again terminated the arrhythmia (100 per cent sinus beats). Elevation of blood pressure either mechanically or with norepinephrine failed to convert the tachycardia to sinus rhythm when air was being inhaled.

Discussion

The experimental tachycardia studied in these experiments differs in several respects from ventricular tachycardia in man. First, it is usually multifocal, whereas the human counterpart is usually unifocal. Second, the sinus rate in the anesthetized dog closely approximates the tachycardia rate, whereas in man there is a twofold to fourfold difference. Third, if left untreated, the induced arrhythmia spontaneously subsides. The experimental tachycardia, on the other hand, is comparable in that it occurs in the setting of myocardial infarction, it is stable for 1 to 2 days, and it responds to therapy with quinidine and procaine amide.[9,10]

The susceptibility of the arrhythmia to termination by barbiturate and morphine, and, as was found in this study, also by chloralose, necessitated the use of vagomimetic drugs or vagal stimulation to bring out the latent ventricular tachycardia in 10 of the dogs. The effectiveness of cholinergic agents in exposing a "latent" tachycardia is undoubtedly the result of deceleration of the S-A nodal pacemaker.

Hypoxia effectively decreased the overall cardiac rate while increasing the percentage of sinus beats. The pressor effect of hypoxia was shown not to be a factor in the restoration of sinus rhythm, since elevation of arterial pressure without hypoxia did not change the percentage of sinus beats, and hypoxia was still effective when a rise in arterial pressure was prevented.

The effect of hypoxia was transient; it lasted only for the duration of exposure, although some reduction in ectopic ventricular activity persisted for longer periods. This differs from the usual permanent conversion seen in man with the use of quinidine.

In a consideration of the relationship between hypoxia and mechanismal disturbances, the so-called oxygen-gradient theory proposed by Brofman and his coworkers is pertinent. This concept was offered in explanation of the occurrence of ventricular fibrillation as the terminal event in patients with myocardial infarc-

Fig. 2. Effects of hypoxia (6.1 per cent oxygen) and the elevation of arterial pressure on ventricular tachycardia.

Table III. The effect of hypoxia before and after crushing of the sinus node in a dog with ventricular tachycardia

Gas inhaled	Over-all rate (beats/min.)	Sinus rate (beats/min.)	Per cent of S.V.* beats
Air (20 min.)	161	160	21.7
8.3% Oxygen (24 min.)	126	126	100.0
Air (20 min.)	157	—	6.3
S-A. node crushed			
Air (20 min.)	172	—	10.0
8.3% Oxygen (13 min.)	115	—	100.0

*The supraventricular beats (S.V.) are of S-A nodal origin before, and of A-V nodal origin after, destruction of the sinus node.

Table IV. Effect of hypoxia on the arterial blood pressure

Dog number	Blood pressure (mm. Hg)								
	Control			*Hypoxia*			*Posthypoxic control*		
	Systolic	*Diastolic*	*Average*	*Systolic*	*Diastolic*	*Average*	*Systolic*	*Diastolic*	*Average*
22	88	45	67	98	51	75	69	41	55
25	120	75	98	118	73	96	126	88	103
27.	130	83	107	201	116	159	124	84	104
31	100	40	70	128	48	88	100	40	70
32	70	40	55	92	49	70	76	46	61
33	123	54	88	139	64	101	127	60	93
39.	70	44	57	130	61	96	71	48	60
40	92	28	60	113	21	67	55	15	35
43.	113	61	87	153	79	116			
49	103	59	81	106	65	86	96	51	74
51.	111	58	85	138	63	100	117	59	88
67.	69	39	53	77	38	58	50	38	44
78	55	30	43	86	54	70	89	50	70
Mean			73.2			90.9			71.4
S.D.			18.7			25.4			

Another result of hypoxia was an elevation of blood pressure. As shown in Table IV, hypoxia exerted a hypertensive effect in 12 of 13 dogs, including both animals (Dogs No. 27 and No. 49) whose tachycardia was not significantly altered by hypoxia. Mixtures with more than 10 per cent oxygen were not effective in raising pressure.

Inasmuch as elevation of blood pressure has been found to be effective in terminating human arrhythmias in some cases,[8] an evaluation of the effect of the elevation of arterial blood pressure was undertaken in experiments with the Lamson reservoir.

The independence of the hypertensive and antiarrhythmic effects of hypoxia is illustrated in Fig. 2. When arterial blood pressure was allowed to rise, 6.1 per cent oxygen converted a ventricular tachycardia to sinus rhythm (0 to 86 per cent sinus beats). When elevation of arterial

Precisely how dangerous the administration of a hypoxic mixture would be during ventricular tachycardia secondary to myocardial infarction in man is not clear from these studies. In healthy adults, mixtures of 7 or 8 per cent oxygen are well tolerated for hours. Whether such hypoxia would further extend the area of damage in an infarcted heart, or impair cardiovascular function in other ways, is not known.

Summary

Ventricular tachycardia produced in dogs by ligation of the anterior descending coronary artery was studied during exposure to hypoxic gas mixtures. Exposure to concentrations of oxygen between 5 and 10 per cent in the inspired air caused a significant increase in the percentage of beats of supraventricular origin. Lower concentrations of oxygen commonly resulted in ventricular fibrillation; higher concentrations were ineffective. The antiarrhythmic effect was shown to be primarily the result of a reduction in the frequency of idioventricular discharge. Elevation of arterial pressure was not a factor.

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tion. Brofman stated that after coronary occlusion a difference in potential exists between areas of poorly oxygenated tissue and adjacent areas of normally perfused muscle. This difference in potential, manifested as displacement of the S-T segment in direct epicardial leads, is presumed to facilitate the generation of idioventricular impulses.

It has been shown that hypoxia reduces the difference in potential between normal myocardial tissue and infarcted areas of heart muscle, as measured by restoration of elevated S-T segments to base-line levels during administration of hypoxic gas mixtures.[1,2] High concentrations of oxygen produce the opposite effect. On the basis of these findings, it has been suggested that the use of oxygen in patients with myocardial infarction may increase the electrical "instability" of the heart.[1]

If the oxygen-gradient theory is valid, i.e., if there is, corresponding to the difference in oxygenation of the various areas of recently infarcted myocardium, an electrical gradient responsible for ventricular fibrillation and, presumably, ventricular tachycardia, then it follows that the administration of hypoxic mixtures to the animal should diminish the electrical gradient and have an antiarrhythmic effect. That such a procedure in this series of dogs did increase the proportion of sinus beats is in accord with the concepts expressed in the oxygen-gradient theory, but does not prove that the theory is valid.

Recently, Badeer[14] concluded that the "oxygen differential" between ischemic and perfused regions of the ventricular myocardium does not play a role in the development of ventricular fibrillation after coronary occlusion. The early incidence of fibrillation after acute coronary ligation was not significantly greater in a group of dogs ventilated with 100 per cent oxygen than in a comparable series exposed to room air. Although it has been stated that the S-T displacement associated with acute infarction in dogs is increased by high concentrations of oxygen (Zao[2]), it seems unlikely that the difference in membrane potential between uninjured and injured portions of the myocardium would be increased by oxygen tensions in excess of that necessary to fully sustain oxidative metabolism. Even though there can be no doubt that the potential gradient and flow of current engendered by ischemic injury must influence the excitability of marginal areas of muscle, it is by no means certain that the flow of current is of itself the trigger which sets off spontaneous activity. Hypoxia also shortens the refractory period of ventricular muscle, and it is possible, therefore, for hypoxic but still viable cells to be re-excited by adjacent normal tissue. Whether the flow of current or the disparity of refractory periods is the prime agency, exposure of the nonischemic area of muscle to hypoxia should be expected to reduce the difference between the perfused and nonperfused tissues, and thus reduce the likelihood of spontaneous activity, even though administration of oxygen in Badeer's experiments did not increase the incidence of ventricular tachycardia and fibrillation.

Maling and Highman[7] exposed dogs to 5.2 per cent oxygen for 3 hours within 2 days after surgically induced myocardial infarction and observed that at least one of the dogs died with ventricular fibrillation. In other dogs exposed to 5.2 or 4.3 per cent oxygen for 3 hours soon after infarction, there was frequent ectopic ventricular activity. This severe degree of hypoxia also commonly resulted in fibrillation in our series. This would suggest that ventricular arrhythmias can be induced as well as suppressed by hypoxia. Although this does not negate the concept that differences in oxygen content in the heart may cause arrhythmias, it suggests that this constitutes only one of several possible mechanisms.

Catecholamines and potassium, both released by myocardial damage and hypoxia, are able to induce ventricular arrhythmias.[11,12] Marked slowing of ventricular conduction which occurs when dogs are exposed to lethal hypoxic mixtures also predisposes to fibrillation.[12,13] These factors may play a part in the induction of ventricular tachycardia.

Conversely, the antiarrhythmic effects of nonlethal degrees of hypoxia on dogs with experimental ventricular tachycardia may be due to the moderate shortening of conduction time noted by Harris and Matlock.[13]

animals of this size and would be sufficient to provide satisfactory counting rates.

All animals were kept under light anesthesia for about 6 hours. A polyethylene catheter was inserted into the jugular or femoral vein to facilitate the frequent sampling of blood. Five per cent dextrose in water was run slowly through the catheter to prevent clotting. After the dogs had recovered from anesthesia, specimens of blood were obtained by direct venipuncture. The weights of the dogs, the doses of digoxin, and other information are shown in Table I.

A disc-type oxygenator and rotary pump, as described by Hara and associates,[6] were utilized for the bypass. A high flow rate was maintained throughout the procedure (90 to 100 c.c. per kilogram per minute or about 2.2 to 2.4 liters per square meter). Each animal was subjected to 30 minutes of extracorporeal circulation. The chest was closed, and, approximately 30 minutes later, 0.5 mg. of H^3-digoxin was injected into a vein distant from the site from which blood was aspirated.

A specimen of blood was obtained before administration of the radioactive material for a background control. After administration of digoxin, specimens of blood were obtained at 5, 10, 15, 20, 30, and 45 minutes; 1, 1½, 2, 2½, 3, 3½, 4, 6, and 12 hours; and daily thereafter for 3 days. The specimens were centrifuged and digoxin was extracted from the blood serum by a method previously described.[4]

Results

The levels of serum radioactivity were plotted against time on semilogarithmic paper, and two exponential curves were derived from the plotted points. Curve B is the best straight line through these points after equilibration. It represents the rate of metabolism and excretion of digoxin. Curve C is derived by subtracting Curve B from the plotted points and represents early distribution and binding of digoxin. Fig. 1 demonstrates these curves for both the control and the bypass studies on Dog No. 6.

The half-lives (length of time necessary for half of the radioactivity that was initially present to disappear from the blood) of both exponential curves of all the animals were determined and are shown in Table II.

Curve C declines much more rapidly

Table I. *Perfusion data*

Dog number	Weight (lb.)	Sex	Digoxin control dose (mg.)	Digoxin bypass dose (mg.)	Mean B.P. (mm. Hg) range on bypass	Blood volume (− or +) on pump (c.c.)	Remarks
1.	37	F	0.75	0.5	75–125	+25	
2.	40	F	0.75	0.5	70–125	+400	
3.	—	F	0.75	—	—	—	Expired prior to bypass
4.	41	F	0.75	0.5	150	+75	
5.	40	F	0.75	0.5	110–165	+750	Heart worms
6.*	40	F	0.75	0.5	85–150	+550	
7.*	35	F	0.75	0.5	95–150	−100	
8.	36	F	—	0.5	110–125	+100	Expired after bypass
9.	38	M	0.5	0.5	95–125	+400	Contaminated specimens
10.	42	M	—	0.5	100–150	—	Expired after bypass
11.*	33	M	0.5	0.5	80–120	+300	
12.	42	M	0.5	0.5	140–150	0	Heart worms
13.	58	M	0.5	0.5	80–125	+2,000	Expired after bypass
14.	34	M	—	0.5	60–150	+900	Expired after bypass
15.*	36	M	0.5	0.5	90–150	+100	
16.*	30	M	0.5	0.5	90–150	+200	
17.*	31	M	0.5	0.5	120–150	+625	

*Control study performed 3 to 4 weeks after bypass.

The effect of cardiopulmonary bypass on the turnover rates of digoxin in the serum of dogs

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The increased use of extracorporeal circulation for intracardiac surgery has demonstrated that care must be exercised if optimum digitalization is achieved and overdigitalization and underdigitalization are to be avoided.[7,8,10]

Our clinical experience has suggested that the majority of patients appear to exhibit increased sensitivity to digitalis and develop toxicity to smaller than usual doses in the immediate postperfusion period.

A similar decreased tolerance to meperidine hydrochloride has been noted after extracorporeal circulation; and Hanks and associates[5] recommended minimal doses (10 to 25 mg.) only when necessary for pain.

Szekely and Wynne[9] have shown that hypothermia decreases the sensitivity to digitalis and, in general, reduces the metabolism of other substances.[3] Although hypothermia is used frequently in conjunction with cardiopulmonary bypass, this report will concern only extracorporeal circulation at normal body temperature, in order that the effect of the bypass alone may be evaluated.

Changes due to alteration in metabolism of drugs may be reflected by changes in the turnover rates of labeled material. In this study, turnover rates of tritiated (H^3-labeled) digoxin* were determined in dogs which had and had not been subjected to extracorporeal circulation.

Materials and methods

Seventeen mongrel dogs were used; their weights varied from 30 to 58 pounds. All animals were anesthetized with either pentobarbital or thiamylal sodium. The control study was made in 6 animals 3 to 4 weeks before the bypass, and in 5 animals 3 to 4 weeks after the bypass.

Tritium (H^3)-labeled digoxin, with a specific activity of 44 μc per milligram, was prepared by the Wilzbach method.†[11] Seven control animals were given 0.75 mg. of H^3-digoxin, and 7 were given 0.5 mg. of H^3-digoxin intravenously. Previous experience had shown that these amounts would not produce digitalis toxicity in

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†New England Nuclear Corporation, Boston, Mass.

role during this period (mean half-time of 11 minutes). The late slope of Curve B is more gradual after the bypass and would be compatible with this hypothesis, since it would be consistent with a lower rate or an alteration in metabolism. Excretion was not studied in this experiment.

These data suggest that there is a primary alteration in the metabolism of digoxin by the body rather than a change in the rate of excretion or increased muscle sensitivity after cardiopulmonary bypass, although the latter factors may have a secondary role.

Browning and associates[1] have demonstrated that there is a decreased tolerance

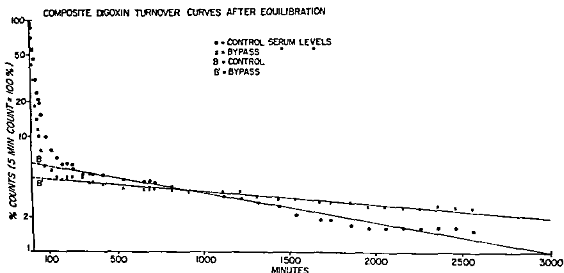


Fig. 2A. Composite of serum turnover curves after equilibration. Five-minute count equals 100 per cent. Differences between Curve B (control experiments) and Curve B' (bypass experiments) are shown. Note the steeper slope of control Curve B, which indicates more rapid late dominant turnover of digoxin, and the transsection of the two curves at about 900 minutes.

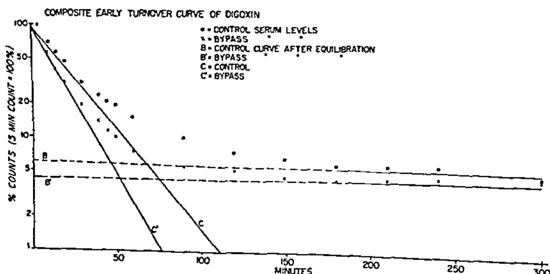


Fig. 2B. Composite of the early portion of the serum turnover curve. Five-minute count equals 100 per cent. The steeper slope of Curve C' (bypass experiments) is shown. This is accompanied by a fall in serum radioactivity below the level of that of the control experiment which persists for 900 minutes.

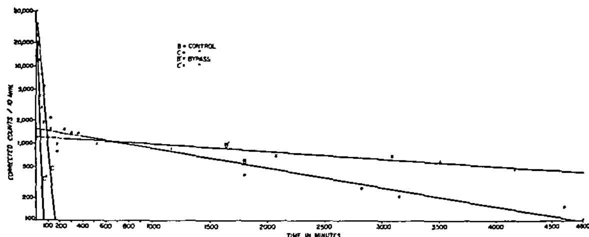


Fig. *1*. Serum turnover of digoxin in Dog No 6 before and after bypass. Curves B and C represent the control study, Curves B′ and C′ represent the bypass study. Note the steeper slope of Curve C′ as compared to Curve C, and the more gradual slope of Curve B′ as compared to Curve B. This illustration is representative of the type of alteration in serum radioactivity curves seen after cardiopulmonary bypass.

in the post-bypass studies and exhibits a mean half-life of 11 minutes, whereas that of the control group is 20 minutes. The data are significant statistically (p 0.01). There is also a striking difference in the B curves of the two groups. The half-life of Curve B of the control group has a much greater slope, approximately one half that of the bypass group (p 0.05). There was no statistically significant difference noted between dogs in which control studies were made 3 to 4 weeks before the bypass and those in which studies were made 3 to 4 weeks after the bypass.

Fig. 2 is a composite graph of all the animals studied. It demonstrates the differences in Curves B and C in the control and bypass groups of all the animals. Levels of radioactivity are graphed as mean per cent of the 5-minute specimen. The more rapid distribution or binding and the slower turnover rates of digoxin in the post-bypass animals are shown.

Determinations of blood pH, serum potassium, and calcium which were made during these experiments failed to reveal significant changes. Blood pressure was monitored in the immediate postperfusion period and was adequately maintained.

Discussion

This study demonstrated two significant findings which offer an explanation for the clinical observation that there is a decreased tolerance to digitalis compounds in the period after extracorporeal circulation. The H^3-digoxin turnover curves in dogs reveal that: (1) digoxin disappears from the blood serum more quickly in the immediate period after bypass, and for the first 15 hours the serum radioactivity is lower than that of the control study; (2) thereafter, the curves separate again, and the levels of digoxin in the blood of the bypass group become higher than those of the control group. These levels remain higher for the period studied, which demonstrates that the dominant turnover rate is slower in the bypass group.

The increased sensitivity to digoxin after extracorporeal circulation might be explained by several mechanisms: (1) increased sensitivity of the heart muscle to digitalis, (2) decreased urinary excretion, or (3) altered metabolism of the drug.

It is interesting that the more rapid disappearance of digoxin is seen in the first 15 hours after extracorporeal circulation. This correlates with the clinical difficulty which is frequently encountered after the administration of digitalis glycosides to patients. The data reveal that during this period of increased sensitivity there is a more rapid decline of radioactive digoxin, and there is less total radioactivity in the blood serum. This indicates an increased tissue binding of the glycoside or a change in the space of distribution, since excretion could play only a minor

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Table II. Serum turnover half-life

Dog number	Curve C		Curve B	
	Control (min.)	Bypass (min.)	Control (min.)	Bypass (min.)
1.	20	10	1,360	6,200
2.	20	10	1,580	6,600
4.	15	15	1,200	2,200
5.	30	10	2,140	5,600
6.	30	10	1,410	4,000
7.	20	15	1,750	1,560
11.	15	10	3,800	3,850
12.	20	10	1,170	1,380
15	21	11	1,690	2,180
16.	17	11	1,280	1,980
17.	14	10	1,325	2,000
Mean	20	11	1,700	3,414

Dogs No. 3, 8, 10, 13, and 14 died during study. The serum of Dog No. 9 was grossly contaminated.

to acetylstrophanthin immediately after cardiopulmonary bypass, but this was not found when the experiment was repeated 24 hours after the bypass. The changes observed in the turnover of serum digoxin after the bypass suggest also that the major detectable alteration is within the first 24 hours.

Lown, Black, and Moore[7] have amply reviewed the shift of electrolytes in the postoperative period and stress the role of an increase in sensitivity to digitalis associated with low levels of intracellular potassium. These changes are frequently not associated with an alteration of serum potassium and are difficult to evaluate in a serum turnover study of this type. Blood pH, serum potassium, and calcium determined in these experiments were not altered; however, these experiments were designed to avoid toxicity.

Ionized calcium and magnesium are also involved in sensitivity of the myocardium to digitalis; but, again, the lack of simple and precise methods for measurement of these elements makes evaluation difficult at this time. Depletion of magnesium, however, is accompanied by increased sensitivity of the heart to digitalis.

The metabolic acidosis which frequently accompanies the normothermic bypass also alters electrolyte distribution and frequently persists for hours after extracorporeal circulation.[2] Information relative to digitalis sensitivity in metabolic acidosis is lacking.[7]

Although significant alterations have been shown to be present between control experiments and bypass experiments, 3 animals exhibited little if any change in the dominant turnover rates of digoxin. However, these animals did demonstrate alterations in the early serum radioactivity which were consistent with the findings in the entire group.

Differences noted in turnover times could not be correlated with the weights of the animals, doses of digoxin, body temperatures, serum electrolytes, pH, or other data.

Summary

Turnover rates of tritium-labeled digoxin in the blood serum were studied in dogs after cardiopulmonary bypass. Two significant alterations in the turnover rates of digoxin were demonstrated after extracorporeal circulation: (1) The early slope of the turnover curve was steeper, and the serum radioactivity was lower for 15 hours after the bypass than for the control. (2) The late slope was flatter and the radioactivity was [illegible] than in the control, observati[illegible] data are consi[illegible] ith an [illegible] response to

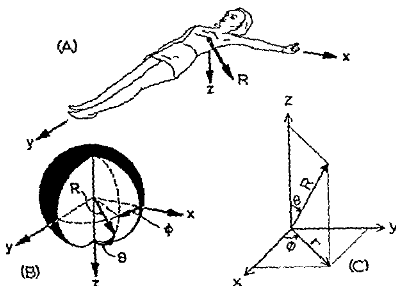


Fig. 1. The relationship between Cartesian coordinates x, y, and z and spherical polar coordinates R, θ, and ϕ. Note that ϕ is Einthoven's angle α, the electrical axis.

parent origin (usually indicated by the brightest part of the figure) coincided with the center of the face of the cathode-ray tube. This adjustment was frequently rendered particularly difficult by the natural tendency of electrocardiographic signals to drift (with respiratory and other movements).

As a result of these studies, it was decided that a "polarcardiograph" should fulfill the following requirements: It should (1) provide the spherical polar coordinates of the heart vector (from signals obtained from a suitable vectorcardiographic lead system applied to the patient), (2) define the origin of the system (according to instructions that might vary from patient to patient), ensuring, through base-line clamping, that this origin was restored in each heart cycle, (3) have a pass-band extending from 0.1 to 200 cycles per second; (4) give angular readings accurate to 5 degrees and magnitude readings to 5 per cent accuracy, (5) yield immediately readable records; (6) be easy for a trained electrocardiographic technician to operate; (7) be sufficiently compact and mobile to be wheeled easily about a hospital by a female technician; (8) provide for simple calibration so that the person who reads the tracings will know that the device was operating correctly when they were taken—a function analogous to that performed by the 1-mv. calibration signal in the conventional electrocardiograph.

A computer which met most of these requirements was described in 1958,[14] but at that time it lacked sufficient stability for clinical use. Subsequent development has resulted in the device described here. It fulfills the above requirements and has been in hospital use since February, 1961. Because it provides (spherical) polar coordinates of the heart vector, it has been termed the *polarcardiograph.*

Principle of operation

The relationship between Cartesian and spherical polar coordinates and the manner in which the coordinate axes are applied to the human subject is shown in Fig. 1. In the frontal, or xy, plane, the frontal angle, ϕ, corresponds to Einthoven's angle α. The polar angle, θ, is the angle the heart vector makes with the z axis; ϕ and θ correspond to longitude and colatitude, respectively. From Fig. 1, *c*, in which the coordinates are rearranged to appear in a more usual representation, we see that $x = r \cos \phi$, $y = r \sin \phi$, $z = R \cos \theta$, and $r = R \sin \theta$, where R and r are, respectively, the spatial and frontal magnitudes of the heart vector.

Now let $v_1 = \sin \omega t$, and $v_2 = \cos \omega t$,

The polarcardiograph. An analogue computer that provides spherical polar coordinates of the heart vector

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A repeated interest in the polar coordinates of the heart vector[1-4] has resulted in the use of various means to compute them from the Cartesian coordinates provided by vectorcardiographic lead systems.[5-7] In addition to the suggestion that a digital computer be used to perform the coordinate transformation,[4] three partial solutions using analogue computers have been described. In 1950, McFee[9] described a "trigonometric computer with electrocardiographic applications" that provided the polar coordinates of the heart vector in two dimensions, but there is no record of the device having been used clinically. He suggested the means by which two such computers could be used to provide spherical coordinates. In 1955, Sayers[10] described an analogue computer that yielded only the spatial magnitude curve of the heart vector, and, in 1958, Abildskov and associates[11] described the use of a computer constructed according to the principle suggested by McFee, which did, in fact, provide true spherical coordinates of the heart vector. The usefulness of this latter device was, however, limited by its bulkiness and the fact that it provided information about the QRS complex only. This would seem to be a severe limitation since the S-T segment and the T wave are often the most sensitive indicators of heart disease.

Whether time-graphs of the heart vector in spherical coordinates are of value in clinical electrocardiography remains to be established because lack of suitable instrumentation has so far prevented the accumulation of sufficient data. Neither has it been shown that such graphs, even if they were valuable, could be conveniently obtained at the patient's bedside. It was the aim of the work herein described to show that this could be done.

To establish the exact clinical requirements and, incidentally, to gain experience in the design of computers of this type, a two-dimensional Cartesian-to-polar analogue transformation device was constructed in 1954,[12] and satisfactory tracings were obtained on about 50 patients. Input signals were obtained from two direct-writing electrocardiographs,[13] and the output was fed to a photographic recorder (Sanborn Twin-Beam). A major difficulty was encountered in this study in defining and maintaining the origin. The vectorcardiographic loop obtained from the two Cartesian inputs was shifted until its ap-

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as those which apply in vectorcardiography, and they drive both the computer and the cathode-ray tube which gives the vectorcardiographic display. Their only special feature is the coupling between the third stage and the fourth or final stage to permit clamping (vide infra). The system has an over-all time constant of about 2 seconds.

Clamping. The necessity for clamping has already been mentioned. The third stage of the amplifier can be represented by the voltage source v_s in series with its internal resistance 2r (Fig. 4). The resistances and capacitances are so proportioned that $rC<10^{-3}$ seconds, and $RC>15$ seconds If S is closed for an interval of several milliseconds while v_s has "base line" potential v_{s0}, a bias is established on the capacitors so that the circuit tends to respond to v_s-v_{s0} for some time (at least one heartbeat) after S is opened. Since closing the switch S forces the corresponding input to the computer to be zero, the desired effect will have been achieved if v_{s0} corresponds to the "isoelectric" level.

To actuate the switch, S, which is a high-speed relay, the steepest (positive or negative) slope in any one of the three x, y, or z signals is selected by the operator, who is guided by the vectorcardiograms which appear on the monitor scope. This signal is differentiated, passed through a sensitivity control available to the operator, and then to an adjustable delay circuit. The output of the clamp-delay circuit is then used to generate a pulse with a duration of approximately 20 milliseconds which actuates the relays. Clamping is indicated by the flashing of a neon light and intensity modulation on the beam of the monitor scope. In operation, the clamp circuit is actuated by the QRS complex of the preceding heartbeat, and the clamp delay is set so that the clamping signal is applied during the resting interval (this commonly follows the T wave, although in some cases in which a prominent U wave is present the clamp may be applied during the P-R interval). If the clamp delay is incorrectly set, the resultant magnitude tracing will be conspicuously distorted and will show an elevated base line during the resting period. A rough indication of the correct setting of the clamp-delay control is provided by the monitor scope: the intensity of the cathode-ray beam increases during the application of the clamp, and by variation of the clamp delay the brightening of the beam can be made to occur at the origin of the vectorcardiographic loop. When this happens, the vectorcardiographic loop is correctly centered. Altogether, three controls require adjustment for the correct setting of the clamp circuit, but in practice this presents little difficulty to the operator.

Oscillator, modulators, and filters. The carrier frequency for all modulators is 4 kilocycles per second—a compromise chosen to avoid the difficulties inherent in phase measurement at high frequencies and to preserve an over-all frequency response to 200 cycles. A stable oscillator produces sine and cosine waves, and the corresponding square waves are obtained by amplifying and clipping.

Addition of the amplitude-modulated sinusoids is achieved by simple resistive networks.

Phase meters. In order that the phase meters may have a large dynamic range, three stages of amplification and clipping are used. For the frontal angle output, the resultant square waves are differentiated and used to drive a bistable flip-flop, as previously described, the output of which is smoothed by the galvanometer which records ϕ. Since the polar angle varies through 180 degrees only, its phase measurement is carried out by addition of the corresponding square waves, followed by rectification, and then smoothing by the galvanometer which records θ. Because the frontal angle may pass through a discontinuity at ±180 degrees during the QRS interval, a galvanometer with a deflection time considerably less than that possessed

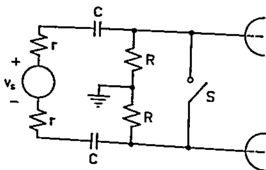


Fig. 4. The clamping circuit for defining the base line.

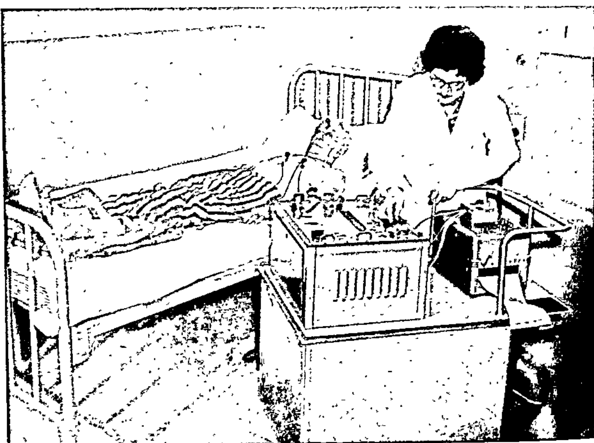


Fig 3. The polarcardiograph

agreement between various interpreters as to the position of the base line, although difficulty would arise in certain cases—for example, in those in which there was a prominent U wave immediately before the succeeding P wave, or in cases in which either the rate was very rapid or the complexes were very much spread out and distorted, as in ventricular tachycardia. It must be emphasized that in any case wherein agreement cannot be reached upon the correct location of the base line, talk of the angular direction of vector components of the heart cycle is meaningless.

In the polarcardiograph the problem of definition of the origin has been left to the operator, but the correctness of her choice is readily apparent to the interpreter of the tracings, since he has only to look at the magnitude output to reassure himself. In appearance, the magnitude output resembles an electrocardiographic tracing and shows P, "QRS," and T components as well as a base line between complexes. When the origin has been correctly defined, all signals reveal themselves as positive displacements, and the "base line" of the magnitude output will be at zero. Otherwise, the "base line" will not be at zero, and, what is much more striking, the tracing may appear to show negative complexes or waves relative to the base line.

General description of the polarcardiograph

The polarcardiograph is carried on a pneumatic-tired trolley. A cabinet which contains the amplifiers, the vectorcardiographic presentation, and the computing circuits rests on the top deck of the trolley (Fig. 3). Beside this cabinet is the recorder (Honeywell Visicorder). The power supplies and cooling fan are mounted beneath.

Amplifiers. The x, y, and z amplifiers are of more or less conventional design and amplify the signals derived from the vectorcardiographic lead system. They are subject to the same design considerations

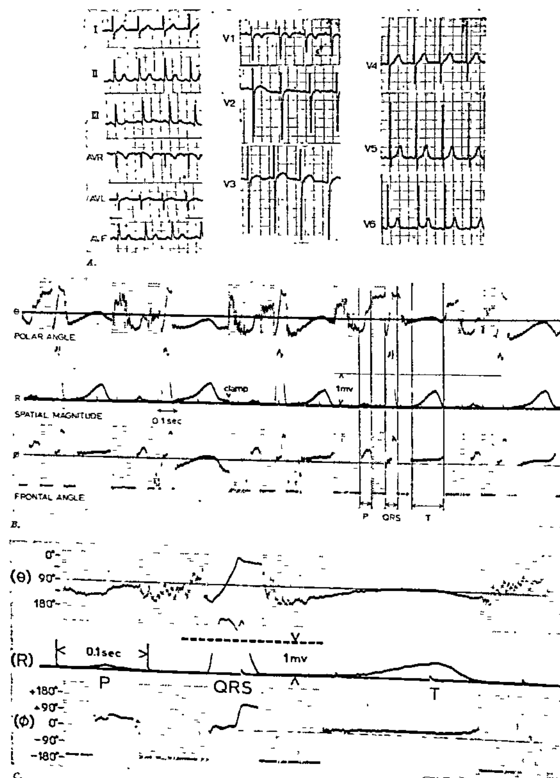


Fig. 6. *A*, 12-lead ECG from a 4-year-old child *B*, Polarcardiogram from the same child. *C*, The same polarcardiogram recorded at 5 times the paper speed used for *B*. Angle tracings at zero magnitude have been shaded to indicate that they have no significance.

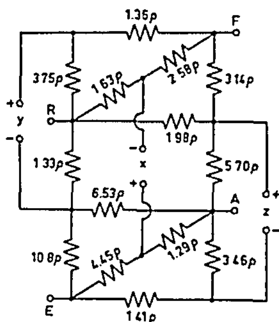


Fig. 5. Improved RAFE network. In the present case ρ = 100 kilohms. In this lead system, *R* and *F* refer to the right arm and the left leg, and *A* and *E* to similarly labeled electrode positions in Frank's system.

by conventional direct-writing recorders is required if significant parts of the QRS frontal angle tracing are not to be lost when the pen swings from one extreme of the scale to the other. To circumvent this difficulty and still obtain immediately readable records, an ultraviolet photographic recorder is used. The galvanometers selected have a natural frequency of 330 cycles per second, which is high enough to record the frontal angle satisfactorily and yet low enough to provide adequate smoothing of the computer outputs.

Calibration. In addition to the usual 1-mv. calibration signals applied to each amplifier input, an automatic calibration check is provided by a stepping relay in such a way that, at the output, the angle tracings change in 45-degree steps while the magnitude stays constant at a value established by 1 mv. at any one of the three inputs or by combinations of x, y, and z calibration signals such that $(x^2 + y^2 + z^2)^{1/2} =$ 1 millivolt. The automatic check can be inscribed at the beginning or end of a record and indicates the state of adjustment of the polarcardiograph to the interpreter as well as to the operator.

Results

The polarcardiograph has been in continual hospital use since February, 1961, and in its first 9 months of operation, approximately 1,200 tracings were taken with it.

In the early stages of its evaluation, it was thought to be desirable to use the simplest possible lead system; thus, the RAFE lead system was employed.[13] The resistance network now used for this lead system is shown in Fig. 5. This was substituted for the network originally described because it conforms better with Frank's image-space data.[14] Upon completion of the early trial, it was decided to include Frank's 7-electrode system[17] because it seemed to be gaining increasing support. It was also thought to be important to distinguish between the trial of a particular lead system and the trial of the polarcardiograph. The results obtained with the two systems will be the subject of future communications.

The choice of the Z axis for the polar axis (Fig. 1) arose out of the fact that the frontal angle, ϕ, corresponds to *Einthoven's* angle α, the electrical axis of the heart. Furthermore, with this choice of axis, correlation of the electrocardiograms with polarcardiograms is facilitated, since the limb leads are most readily obtained from frontal plane vectorcardiographic loops. However, there is evidence to suggest that the Y axis may prove to be more valuable as the polar axis. This is due to the fact that the normal transverse QRS loop is always inscribed in a counterclockwise direction, whereas the normal frontal QRS loop may be inscribed in either a clockwise or a counterclockwise direction or even show a figure-of-eight pattern. The sense of inscription in the plane normal to the polar axis is indicated by the direction of variation of ϕ. This means that with a Z polar axis, ϕ may normally increase or decrease during the QRS, but with a Y polar axis, ϕ will, in normal tracings, be monotonic—it will only decrease. Therefore, abnormalities in the direction of inscription of the transverse loop should readily reveal themselves in the ϕ tracing with a Y polar axis. Results obtained from patients with anterior infarction support this expectation. At the

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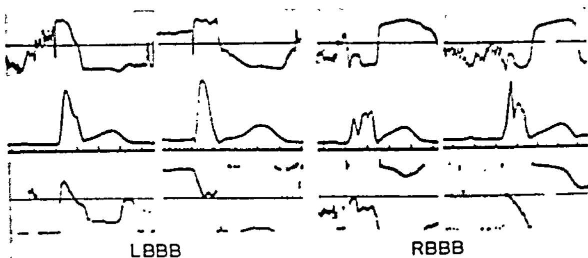


Fig. 7. The polarcardiograms from two cases of left bundle branch block and from two cases of right bundle branch block.

present time by means of a system of switching, R, θ and ϕ are recorded with a posteroanterior Z polar axis and, immediately following, with a longitudinal Y polar axis.

Fig. 6,*B* illustrates the repetitive nature of the records obtained with the polarcardiograph, taken in this case from a 4-year-old child whose 12-lead electrocardiogram is also shown (Fig. 6,*A*). The variation in the shape of the peaks of the magnitude tracing is due to the patient. The irregularities in the angle tracings occur only when the magnitude is zero, and have no significance. The base-line-restoring effect of the clamp may be seen after the second T wave. Fig. 6,*C* shows polarcardiograms from the same patient, using an expanded time scale.

As an example of the possible usefulness of the instrument in diagnosis, records from two cases each of left and right bundle branch block are presented in Fig. 7. In all cases the duration of the QRS is seen to be greater than 0.1 second, but in LBBB the contour of the spatial magnitude curve during the QRS interval is generally smooth, whereas in RBBB it is generally jagged, with several spikes. In LBBB the polar angle is in the range of 0 to 45 degrees during the QRS, but in RBBB it is in the range of 90 to 180 degrees. The frontal angle tracing indicates that in LBBB the heart vector points to the left at the terminal part of the QRS, whereas in RBBB it points terminally to the right.

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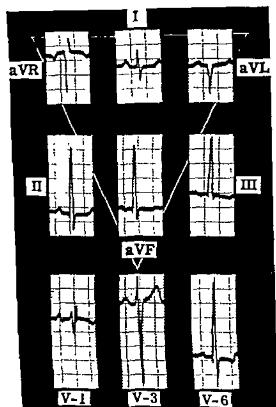


Fig. 1. Electrocardiogram in a case of left ventricular-right atrial canal and subaortic stenosis. The tracing shows tall P waves in Leads I and V_1, prolonged P-R interval, right bundle-branch block, and biventricular hypertrophy

murmur, different in quality from the one described, was heard at the left sternal border at the level of the third and fourth intercostal spaces and over the aortic area. Propagation of this murmur into the cervical area occurred. The second cardiac sound at the pulmonary area was accentuated and split. A systolic ejection click, best heard over the left lower parasternal area, was evident. The blood pressure measured 100/80 mm. Hg.

Roentgenographic examination revealed a mild increase in prominence of the pulmonary vascular markings as compared with the findings made at examination when the patient was 6 years old.

The electrocardiogram showed a sinus rhythm with peaked, elevated P waves, a complete bundle-branch block, and evidence of biventricular hypertrophy. There was also biphasic T wave over the precordial position V_6 (Fig. 1).

Catheterization of the right side of the heart (Table I) revealed evidence of increased oxygen content in the blood of the right atrium and a further increase at the right ventricular level. There was mild elevation of right ventricular pressure. Calculation of the left-to-right shunt indicated that the pulmonary flow was 2.2 times the systemic flow. The systemic arterial saturation was complete. A diagnosis of ventricular septal defect was suggested, although the possibility of aortic stenosis or coarctation were considered to be additional conditions on the basis of clinical findings compatible with either. In order to resolve this, recommendation was made for a catheterization of the left side of the heart

During the last admission (in 1961) the physical findings were similar to those of the previous examination. Catheterization of the left side of the heart and angiocardiography were performed by means of a catheter inserted into the left ventricle percutaneously through the thoracic wall.[3] The study showed the left ventricular pressure to be 190/0 (end-diastolic pressure of 20) mm Hg, and the aortic pressure measured 90/70 mm Hg (Fig. 2). The selective angiocardiography revealed evidence of a left ventricular-right atrial canal and of subaortic stenosis. The basis for this conclusion was derived from the fact that radiopaque material injected into the left ventricle showed almost simultaneous opacification of the left ventricle and the right atrium. The subaortic area of the left ventricle was visualized as a constricted area which did not change in size during the cardiac cycle (Fig. 3). The aortic valve did not appear to be stenotic, although there was evidence that it had a bicuspid nature.

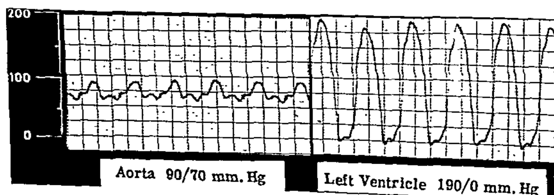


Fig. 2. Aortic and left ventricular tracings. The aortic curve is of stenotic type with delayed "time to peak" (0.22 second). The systolic gradient at rest between the aorta and the left ventricle of 100 mm. Hg is evident.

Case reports

Left ventricular—right atrial canal and subaortic stenosis. Report of a case diagnosed preoperatively

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Among the uncommon forms of congenital intracardiac shunts is a communication between the left ventricle and the right atrium. The association of subaortic stenosis with this type of shunt is almost unique; to our knowledge, only one reported case exists. In that case the correct diagnosis had been made at necropsy.[1]

In a case of this combination, which we report here, the clinical diagnosis was made by the use of selective left ventriculography and appropriate pressure studies. Surgical treatment was successful in closing the abnormal communication and in partial relief of the subaortic stenosis.

It is the purpose of this report to describe the clinical and diagnostic features and the surgical techniques employed as well as to suggest an explanation for the development of the peculiar complex encountered.

Case report

A 13-year-old girl was admitted to the University of Minnesota Hospitals on Nov. 6, 1961, for reevaluation of a known congenital cardiac lesion.

A cardiac murmur had first been noted when the patient was 2 years old. At that time, no cyanosis, dyspnea, or cardiac enlargement were evident, although a history of frequent epistaxis and colds was elicited.

The patient was first hospitalized when she was 6 years old. The physical examination showed that the child had had normal growth development and was in no apparent distress. The cardiac impulse was at the midclavicular line and slightly increased in nature. A systolic thrill was palpable over the precordium, a systolic murmur was heard at the apex of the heart, at the right lower sternal border and over the aortic area. Plain roentgenograms showed evidence of slight enlargement of each cardiac chamber. The pulmonary arterial segment was somewhat more prominent than normal, and there was evidence of a mild increase in the peripheral pulmonary vascular markings. The electrocardiogram showed evidence of right ventricular hypertrophy and of a complete right bundle-branch block. Although no definite diagnosis was established, the clinical impression at that time favored a ventricular septal defect with possible pulmonary hypertension.

The patient returned to the hospital in 1956, when she was 8 years old, for catheterization of the right side of the heart. The apical impulse was then noted at the fifth left intercostal space near the anterior axillary line, and was heaving in nature. A pronounced systolic thrill was evident over the entire precordium and in the suprasternal notch. A harsh Grade 4 (on the basis of 1 to 4) pansystolic murmur was evident over the entire precordium, with maximal intensity at the cardiac apex and over the right sternal border at the level of the fourth intercostal space. Additionally, a systolic

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Discussion

Left ventricular–right atrial communication has been reported in the past as a curiosity,[3] and has usually been identified at necropsy.[4] More recently, with the successful use of cardiopulmonary bypass and open-heart operation, this lesion has become recognized more frequently during life.[5-7]

Anatomically, the left ventricular–right atrial communication has been divided basically into two groups according to the involvement of the tricuspid valve.[4] In some of the cases the defect lies in the uppermost part of the atrioventricular membranous septum, which results in a direct communication between the left ventricle and right atrium above the normal tricuspid valve. In other instances the defect is situated somewhat lower in the membranous portion of the septum, which allows direct communication between the left ventricle and right atrium, across a deformed septal leaflet of the tricuspid valve. In both conditions, however, the essential hemodynamics remain similar, depending upon the size of the defect and the presence or degree of tricuspid insufficiency. The tricuspid involvement in this anomaly has been frequent and various. Among the 10 cases of left ventricular–right atrial canal operated upon in our institution, in 5 the tricuspid valve was normal, and in the other 5 it was deformed, cleft, or perforated. In 2 of our cases and in 1 reported by Braunwald and Morrow,[7] a small ventricular septal defect was present in addition to the left ventricular–right atrial canal.

Improved diagnostic technique and appropriate surgical correction in subaortic stenosis have aroused increased interest in this anomaly. Hitherto thought to be a rare entity, the diagnosis has been made with increasing frequency by means of catheterization of the left side of the heart or at operation.[8]

The combination of both anomalies, subaortic stenosis and left ventricular–right atrial communication, was reported by Ferencz[1] in 1957. A 26-month-old baby girl with the preoperative diagnosis of mitral insufficiency and aortic stenosis was found at necropsy to have a small high septal defect which allowed communication between the left ventricle and the right atrium. In addition, there was a cleft mitral valve and anomalous chordae tendineae. The latter were attached to the outflow tract of the left ventricle beneath the aortic valve, causing the subaortic stenosis.

Our case, in certain aspects, was similar to that reported by Ferencz. There was left ventricular–right atrial canal and subaortic stenosis but normal atrioventricular valves, without mitral or tricuspid insufficiency (Fig. 4). The subaortic constricted area was composed of fibrous tissue and cardiac muscle below the communication between the left ventricle and right atrium, which did not compromise the mitral orifice. The major component of the subaortic obstruction seemed to be formed by part of the septum, which bulged and encircled the left ventricular outflow tract. There were no anomalous chordae or papillary muscles.

Developmental anomalies of both ventricular outflow tracts have been emphasized frequently. All the component parts at this complex region, such as the muscular septum from below, the atrioventricular cushions, which take off apart and away from the middle portion, and the truncus septum which divides the great vessels, must follow proper direction, must meet in time and place, and, finally, must coordinate with the rapidly growing heart. Patten[9] has emphasized all those factors in the formation of congenital malformations

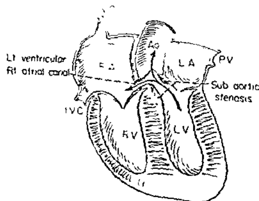


Fig. 4. Schematic drawing which illustrates the anomaly of left ventricular–right atrial canal and subaortic stenosis.

Familial bundle branch block

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Various forms of familial heart disease are on record. Morquio, in 1901, reported on 5 brothers with atrioventricular conduction disturbances. In 1903, Osler[1] described a family with slow pulse rates and Stokes-Adams attacks. Aylward,[2] in 1928, described 2 sisters who had total atrioventricular block. Wallgren and Winblad,[3] in 1938, investigated a family in which 2 out of 5 siblings had congenital heart disease; one had a complete heart block, whereas the father and the other members showed evidence of conduction disturbances. In a family with complete heart block observed by Wendkos and Study,[4] in 1947, it was noted that the parents also had conduction disturbances. Various degrees of atrioventricular conduction disturbances with familial incidence have been described by Stéphan,[5] Fulton, and Canabal and Dighiero.[6] Familial cardiomegaly has been described by Evans[7]; and Paulley and associates[8] submitted a well-documented report on 3 affected siblings with pathologic similarity at necropsy. Battersby and Glenner[9] described a sibship of which 5 members had an identical cardiomyopathy, some with conduction defects.

We recently had the opportunity of investigating another type of conduction disturbance, in which all 4 siblings of a family revealed varying degrees of right bundle branch block. No other evidence of disease could be found.

Case reports

The 4 children were brought for investigation by the father shortly after the death of his wife. His wife's parents had both died suddenly in their early

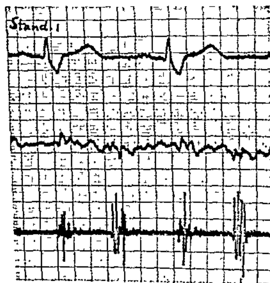


Fig. *1.* Standard Lead I with phonocardiogram (*bottom trace*) revealing systolic murmur.

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at that portion of the heart, with particular stress to the matter of "timing."

Although there is not, at present, acceptable embryologic grounds for an adequate explanation of the majority of cases with subaortic stenosis, in the case which we have discussed here some suggestions in this regard could be made. Greenberg and Simon[10] reported a case of subaortic stenosis with striking prominence of the ventricular septum toward the left ventricular outflow tract. Embryologically, false direction of the ventricular septum toward the left was suggested.[11] If this does occur, *one may well also expect a lack of an appropriate union of the dividing* septum with the structures above (floor of the right atrium), which results in a combination of two anomalies, namely, subaortic stenosis and left ventricular-right atrial canal.

The diagnosis in this case was based upon catheterization of the left side of the heart. The anatomic findings as observed during operation (site of maximal subaortic obstruction and the septal defect) may well support the theory for common embryologic maldevelopment in this rare anomaly.

Summary

A report is made of a rare case of a congenital heart anomaly which consists of subaortic stenosis and left ventricular-right atrial canal.

Preoperative diagnosis was accurately made by catheterization of the left side of the heart and angiocardiography.

The patient was operated upon by means of the cardiopulmonary bypass technique. The diagnosis was confirmed. The septal defect was closed and the subaortic stenosis partially relieved.

A single embryologic basis as a cause for both malformations (false route of the ventricular septum toward the left) is suggested for this particular congenital entity.

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thirties, one of her brothers has heart trouble designated as a conduction disturbance, another brother has dextrocardia, and the other 3 siblings are apparently normal. His wife had died during an attack of heart block at the age of 35 years. Her record, which was obtained subsequently, revealed that she had been seen at an antenatal clinic 6 years prior to her death. At that time the pulse rate had been 80 per minute, the blood pressure was 130/90 mm. Hg, and nothing abnormal was detected. Minor ailments without cardiovascular involvement were recorded subsequently. A year before her death she had been hospitalized while in a Stokes-Adams attack; the electrocardiogram revealed total atrioventricular dissociation with a probable complete right bundle branch block. A roentgenogram revealed that the size and configuration of the heart were normal. Approximately a year later she died in a Stokes-Adams attack. A necropsy was not performed.

The 4 siblings (B. B., a 12-year-old girl; M. B., an 11-year-old girl; C. B., a 6-year-old girl; and P. B., a 4-year-old boy) were subjectively healthy, and, on questioning, had no symptoms referable to the cardiovascular system. On examination, the pulse rates and blood pressures were normal in all 4. They all had a mid-systolic, Grade 1-2, ejection murmur at the base of the heart to the left of the sternum. In some, fixed splitting, and in others, fairly wide splitting, could be heard over the second intercostal space to the left of the sternum (See Fig. 1.) The rest of the physical examination revealed no abnormality in general build, systems, or organs.

The electrocardiograms of the 4 siblings (Fig. 2) revealed mild to gross right bundle branch block. In C. B., the tracing was only suggestive of right bundle branch block.

The physical examination and the electrocardiogram of the father, who was 36 years old, revealed no abnormality (Fig. 3).

The electrocardiogram of the mother obtained a year previous to her death revealed total atrioventricular dissociation and probable right bundle branch block (Fig. 4).

Roentgenograms of the 4 siblings indicated no abnormality.

The eldest child (B. B.) very willingly submitted to a cardiac catheterization of the right side of the heart, during which no evidence of abnormal pressures or shunts could be elicited.

Discussion

The mother and 4 young siblings of this family revealed an almost identical conduction defect: right bundle branch block was common to all, with the mother developing a complete atrioventricular dissociation. This is apparently a very rare observation, since we could find no report of a similar group. The basis of the abnormality can as yet be only a matter of conjecture. No history or findings suggestive of a rheumatic process, a viral myocarditis, or an ischemic process are at hand. Apparently, the abnormality is restricted to a section of the conducting system in which a genetic defect may be

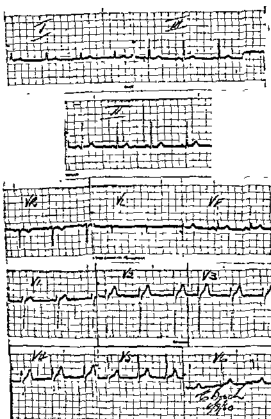


Fig. 3. Electrocardiographic tracing of the father, showing normal picture.

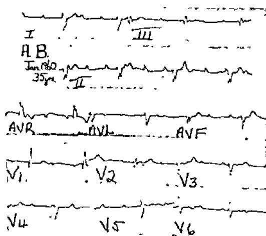


Fig. 4. Electrocardiographic tracing of mother, revealing total atrioventricular dissociation and right bundle branch block.

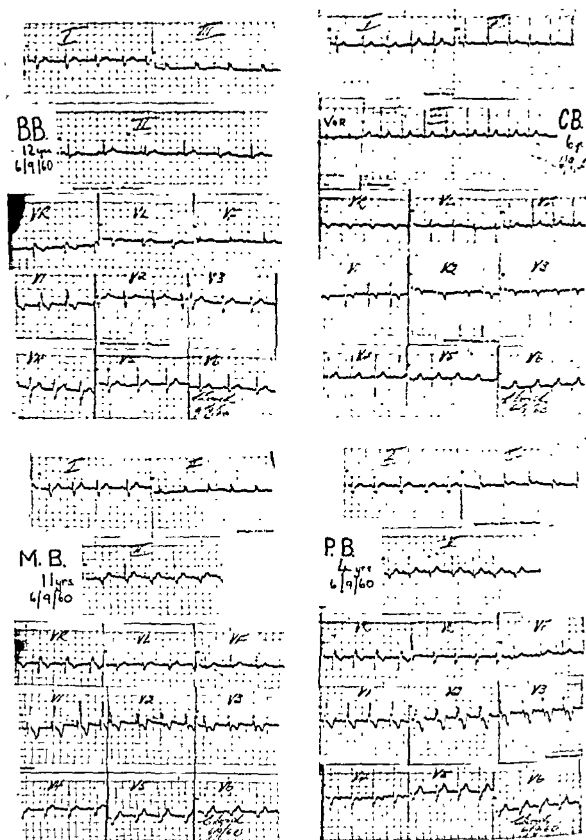


Fig. 2. Electrocardiographic tracings of the 4 siblings, revealing right bundle branch block.

Review

Digitalis assay

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PART I

The purpose of this paper is to review critically the literature on techniques of digitalis assay and to propose a clinical assay method based upon theoretical considerations.

Since the advent of the use of digitalis in the treatment of congestive heart failure, various derivatives and allied compounds have been the object of investigation in an endeavor to find one which would provide the maximum therapeutic effect with the least toxicity. With the extraction and now widespread use of the various digitalis glycosides that are the active constituents of their plant sources, a certain proportion of the local irritative effect of digitalis has been eliminated. However, true cardiac and other systemic toxicity invariably will occur with any digitalis preparation when sufficient drug is administered. It must be recognized that a preparation which will not cause digitalis poisoning when given in excess is also one which will not exert any therapeutic effect.[1] The choice of a preparation can never eliminate the occurrence of toxicity.[2,3]

Investigation of a new drug is restricted to the laboratory or to the human subject. For many years, animal bioassay has been the basis for convenient comparison of digitalis preparations. Innumerable papers have been written on animal assay. In 1909, Houghton and Hamilton[4] outlined the use of the frog method of bioassay of digitalis. Over the next few years, other animals were used in an effort to increase the sensitivity of the tests. In addition, numerous modifications were advocated, all designed to enhance the accuracy of bioassay techniques.[5-18]

Reports appeared which illustrated marked discrepancies in bioassay results associated with types of anesthesia,[19-24] concentration and time of infusion,[22,25-28,37] season,[29] spinal preparations,[30] activity,[31] and different animals.[13,18,24,25,32-39]

Moe and Visscher[40] proposed adoption of a modified dog heart-lung preparation as a means of bioassay, after Peters and Visscher[41] had indicated that there was no assurance that the lethal and therapeutic ratio for all digitalis drugs was the same. In their report of 1938,[40] they reiterated that all bioassays involved toxic doses, and were based on the "tacit assumption that therapeutically useful properties will vary in a direct proportion to the toxic ones." They were able to show differences between lanatosides A, B, and C, in the doses which caused an increased effect and in those which produced cardiac irregularities. Their study proved to be controversial, and Gold and associates[42-44] continued to claim that there were no qualitative differences among the digitalis preparations as a group.

DeGraff, Paff, and Lehman[45,46] thought that prevalent bioassay techniques failed to consider long-acting and short-acting

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present, either as a structural fault in the conducting bundle or possibly merely as a biochemical enzyme derangement in the fibers of the right bundle branch.

Follow-up studies of the children, who are being kept under observation, might throw a more revealing light on this intriguing familial abnormality.

Summary

A description is given of a mother who died at the age of 35 years, and of 4 young siblings, all of whom revealed right bundle branch block as an isolated finding.

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as means of comparing the potency of digitalis preparations in man." However, a review of their data revealed that from 3 to 12 cat units of digitalis to 1 of Digitaline Nativelle caused equivalent effects.

In 1941, in a comprehensive study, Geiger, Blaney, and Druckemiller[77] attempted to "learn whether any reasonably reliable and useful *quantitative* relationships exists with respect to electrocardiographic changes accompanying the *clinical* use of the drug in *therapeutic doses.*" They carefully selected 50 cardiac patients whose electrocardiograms would be relatively free from RS-T and T-wave abnormalities. They found that typical changes in the RS-T segment occurred in less than one half of the patients, and that such changes were neither constant nor uniform accompaniments to the administration of digitalis, nor were they quantitatively indicative of the amount of digitalis given. Gold and co-workers[78-80] continued to recommend electrocardiographic assay. Of 1,500 patients in their clinic, they selected 97 who had no heart failure and regular sinus rhythm. Of these patients with over 1,000 electrocardiograms, only 18 proved to be satisfactory for their studies. An increment of 25 per cent in digitalis dosage could be detected in this group.

Eichna, Taube and DeGraff[81] serially determined the cardiac output by ballistocardiogram and followed the electrocardiogram after intravenous digitalis in a small number of normal patients. They noted no relationship between the electrocardiogram and hemodynamic effects. In 1942, DeGraff[82] reported that he was unable to find any constant relationship between the therapeutic and toxic doses of digitalis and electrocardiographic changes. Dearing and associates[83] studied calculated therapeutic doses of digitalis and found that the electrocardiogram was of no value for bioassay. Gold and associates[84] drew up a cumulative distribution curve for man based on the T-wave changes of the electrocardiogram. They reported that their curve supplied a standard which could be used in the human method of assay of digitalis. Their technique avoided some of the defects of animal assay, but it was open to serious criticisms. Primarily, it was based on the unwarranted and incorrect assumption that changes produced in the electrical systole paralleled those of mechanical systole. Regardless, the authors were still unable to differentiate 25 per cent increments in digitalis dosage. We agree with Dragstedt[85] that this approach would not satisfy the principles of a sound scientific assay, since it is known that persistence of cardiac effects could be quite different from two preparations which have the same effect on the electrocardiogram, and that the drugs would not necessarily be given in the same dosages to maintain digitalization.

It has been our experience, and the experience of others, that the electrocardiograms of cardiac patients on maintenance therapy do not demonstrate quantitative changes associated with variations in the digitalis dosage, despite obvious clinical effects.

Chemical assay

Chemical evaluation of digitalis has been attempted since it was found that a color, dependent upon the lactone group in the glycoside, developed with the Baljet reaction. Knudson and Dresbach[86] used the Baljet chemical reaction to assay specimens of digitalis. These workers used small numbers of cats for comparative bioassay, and accepted a variation of under 30 per cent from the average minimum lethal dose, using the Hatcher and Brody technique. They found an agreement in 23 of the 25 specimens tested. Bell and Krantz[87,88] found that their chemical results paralleled those of the cat method. Vos and Welsh[89] reported that the method was unreliable when compared with the U.S.P. X11 method. Danow, Mathieson and Hays[90] confirmed that the chemical method measured about 70 per cent of the biologic potency. At the present time, chemical bioassay, despite improvements, is considered to be unreliable.[91,92]

Human assay

In 1915, Eggleston[7] reported on an extensive 2-year clinical study of four digitalis preparations. Although he did not investigate the relative merits of each drug, he was able to guide the practitioner as to the approximate amounts of each to administer. In 1924, Luten[93] in a careful study

drugs, and varied with anesthesia and rates of infusion. They attempted to circumvent these failings by the utilization of the isolated chick heart.[47] They were able to demonstrate a closer relationship between clinical and bioassay results, testing digoxin and lanatoside C, than had been obtained in the cat or frog. However, this technique did not consider absorption, latent period of action, cumulation, dissipation, or vagal effect, and was not considered to be a marked improvement.[48-52]

In an extensive paper published in 1943,[53] Moe reviewed the subject and criticized all established bioassays since they were based upon the toxic and not the therapeutic effects of the drugs. All methods assumed that a constant ratio existed between toxic activity and therapeutic activity. Under the circumstances, this could be justified only if all the glycosides were inactivated at the same rate, if toxic action was solely a direct cardiac one, and if all possessed the same toxic therapeutic ratio. The first premise was obviously false. The second was unjustified, since it is known that the lethal effect of digitalis bodies was in part mediated or modified through the central nervous system, as demonstrable in animals under different anesthetics. He attempted to demonstrate a variation in the toxic therapeutic ratio for three glycosides in isolated hearts of cats and rabbits. Using his own criteria for therapeutic and toxic end points, he found different ratios for the three glycosides. However, the ratio for each drug was about the same in the animals as in the dog heart-lung preparation. Although he believed that his results could not be transferred to human beings, he thought that the heart would probably be affected to different degrees by glycosides of a different molecular configuration.

In 1944 Bliss,[54] reporting on the U.S.P. collaborative cat assays, concluded that "the clinical oral potency of purified digitalis preparations cannot be predicted from cat assays alone." Gold[55] affirmed that "the intravenous method does not distinguish absorbable from nonabsorbable materials."

The electrocardiogram and bioassay

As early as 1915, Cohn, Fraser, and Jamieson[56] observed definite changes in the electrocardiograms of patients on digitalis. They believed that these alterations could be a sign that an influence by digitalis was being exerted on the heart.[57] Numerous papers have confirmed their observation.[58-69]

One of the earliest attempts at human assay was by Wedd, in 1919.[70] He studied two biologically standardized tinctures of approximately equal potency. Although his work was inadequately controlled, he did attempt to demonstrate a difference in absorption by noting changes in the T waves of the electrocardiogram. Eggleston and Wyckoff[71] studied the effect of fractions of digitalis, utilizing the first appearance of any electrocardiographic effect as an index of absorption. In 1923, Pardee[72] attempted to use the electrocardiogram to evaluate the potency of four tinctures of digitalis. He reported some correlation in a small number of patients. Although the method impressed him as theoretically valuable, he concluded that it would "always remain true that the final test of the value of a drug is its therapeutic effects on the patient."

Langly,[73] in 1928, gave a single massive dose of digitalis to 80 patients with auricular fibrillation and followed the ventricular rate, changes in the T waves, and toxic symptoms. His results convinced him of the need for a more reliable bioassay.

In 1931, Berliner[74] reported on the effect of digitalis on the Q-T interval of 21 patients. He found that the shortening was not proportionate to the amount of digitalis taken, or to the clinical effect observed. Dieuaide and associates[75] confirmed Berliner's findings.

In 1940, Gold[76] reported a study of 30 patients: 14 had normal sinus rhythm, and 2 were in congestive heart failure; of the other 16 with auricular fibrillation, 8 had congestive heart failure. Those with regular sinus rhythm were given a fixed daily dose of a preparation for 7 days, and the changes in the RT-T segment of the electrocardiogram were followed. After 3 to 4 weeks another dosage was similarly evaluated by changes in the ventricular rate. The authors concluded that the "changes in the T-wave of the electrocardiogram in patients with regular sinus rhythm can be used interchangeably with changes in the ventricular rate in patients with auricular fibrillation

PART II

The first part of this review concluded that no reliable bioassay for digitalis is currently available or universally applicable to human beings. Part II will be devoted to presenting a method for human assay of digitalis, and the application of this technique in the evaluation of gitalin based upon 2 years of clinical experiments.

Review of gitalin

Kraft,[104] in 1912, extracted digitalis leaf with cold water and then chloroform. He named the chloroform - soluble fraction *gitalin*. This fraction, known also as verodigin, Digitol, or Gitaligin, consists of an amorphous white powder with a neutral reaction, soluble in six hundred parts of cold water. Von Straub and Krehl[105] reported that the drug could be discontinued after a short course of treatment. Most of the foreign literature was almost as enthusiastic about gitalin.[106-109]

In 1920, Hatcher[110] analyzed gitalin and found that 1.0 mg. was equivalent to .35 to .5 mg. of digitoxin by cat assay. Haag and Hatcher[111] found that the purified chloroformic residue consisted of gitalin, with small amounts of digitalin, digitoxin, and free genins of the gitalin group, together with other impurities. Although the cat unit of gitalin has been reported to vary from .43 to 1.25 mg.,[18,45,110-114] the average of all reported assays was 0.8 mg.

Bell and Krantz[115] found that gitalin was unique, in that it had "definitely the lowest degree of activity toward the Baljet reaction."

In 1956, Haack and associates[114] analyzed gitalin and identified large amounts of a heretofore unknown cardiac glycoside called *gitaloxin*. This is identical with gitoxin, except that the hydroxyl on carbon 15 of gitoxin is esterified with formic acid. Formylation of the hydroxyl was found to increase potency markedly. However, the formylesters undergo spontaneous hydrolysis to gitoxin unless absolutely dry. Aqueous, alcoholic, alkaline media, heat, time, and other agents promoted hydrolytic degradation. Therefore, this new knowledge should be considered when one assesses studies which did not consider this problem.

Stroud and associates[112] reviewed the literature through 1934. They gave gitalin to 14 ambulatory patients with auricular fibrillation, and found that 0.25 mg. was the approximate equivalent in 2 patients maintained on 1.8 Gm., and in 3 patients who received 0.9 Gm., of digitalis leaf. Obviously, their studies revealed no definite ratio between the dose of each drug causing similar effects.

In 1938, Levy and Boas[116] reported their experience with 36 ambulant patients with auricular fibrillation who were given alternate courses of gitalin and digitalis tablets, with adjustment of the dose to obtain the same heart rate. They were able to establish maintenance doses in 27 patients. It is interesting that when digitalis was discontinued in 8 patients, none developed heart failure. In the others, the only change was a rise in the ventricular rate. Obviously, these patients had an extremely mild heart condition. These investigators concluded that .37 mg. of gitalin was equal to .1 Gm. of digitalis leaf. As for the constancy of any relationship which existed between equivalent therapeutic doses of the two drugs, the ratio in terms of milligrams of gitalin to grams of digitalis varied from 2.4 to 7.5 in 27 patients. Gold[35] reported that gitalin was clinically one third as potent as Digitaline Nativelle on a weight basis.

In view of the conflicting reports of European and American investigators, Batterman, DeGraff and associates[117] undertook the re-evaluation of gitalin and found that when the minimum maintenance dose of gitalin was doubled, 41 per cent of the patients developed toxic symptoms, in comparison to 63 per cent for digoxin, digitoxin, and lanatoside C.

Gold and associates, in their reports of similar studies, were not able to be as certain of the minimal therapeutic doses. Their figures for the incidence of toxicity when the dose was doubled were: digitalis, 38.4 per cent,[76] Digitaline Nativelle, 46 per cent,[76] and lanatoside C, 50 per cent.[75] Batterman and co-workers[118,119] were able to determine the minimal maintenance dose of gitalin in 30 of 46 patients. In this group, 73 per cent were controlled with 0.5 mg. Yet from their table which illustrates the predictability of obtaining maintenance or toxicity, a dose of 1.0 mg. (double 0.5 mg.)

of 4 patients with regular sinus rhythm and congestive heart failure, clearly proved the efficacy of digitalis in patients with slow ventricular rates.

One of the serious errors in the early clinical studies was the failure of investigators to appreciate the chiefly vagal action of small doses of digitalis in the evaluation of changes in heart rates.[94-96] Gold, in 1939, and others[97-99] emphasized that only in the patient with advanced heart failure would the ventricular slowing probably be due solely to the extravagal action of digitalis. Gold clearly demonstrated the errors of comparison when small doses of digitalis were utilized and the pulse rate was followed as the criterion of the effectiveness of digitalis, since atropine could abolish this effect.[97]

Gold and co-workers[100] evaluated lanatoside C and digitalis in 67 patients, all but 9 of whom were ambulatory, but gave no description of their state of cardiac compensation. The maintenance of a ventricular rate between 60 and 80 per minute without the production of toxicity was considered to be a therapeutic dose. Of the 15 cases charted, duration of therapy was frequently less than 4 weeks. Review of their figures showed a variation in the ratio of the drugs from 1 to 3 cat units. After giving therapeutic doses, and then doubling the dose, they found that nearly half of the patients developed toxic symptoms with three digitalis preparations tested. They concluded that therapeutic or toxic end points served equally satisfactorily for assay purposes.[44,76,100]

Despite all of the obvious difficulties and conflicting statements, the earliest criticism of the transference of the results of the methods to human beings was made by Butler[101] in a letter to the editor of the *Journal of the American Medical Association*, in 1939. He succinctly summarized the defects which were, and still are, overlooked by many investigators He pointed out that "a biologic assay is usually performed to determine therapeutic effectiveness in man." He strongly criticized the failure to realize that "a dose of a short-acting glucoside and a dose of a long-acting glucoside which are equivalent in the cat assay will obviously not be equivalent in maintaining digitalization in a patient." He also denounced the unwarranted assumption that the active principles were in the same proportion in all digitalis preparations.

In the following year, Gold[76] concluded that there was sufficient evidence available to state that digitalis dosage in human beings could not be based on the prevailing animal assay values.

In 1941, Gold and co-workers[10] reported that bioassay was necessary because most digitalis preparations were not pure principles. They agreed that bioassay techniques measured a toxic action, but thought that "the search for a therapeutic end point for the assay of digitalis in animals doesn't seem to be very important, however, because the therapeutic and toxic effects of digitalis are due to the same action, and there is no good evidence for a significant difference in the ratio of the doses exciting toxic and therapeutic actions."

Dragstedt,[102] in 1942, reiterated "the necessary discrepancy between such units of biologic activity and therapeutic potency when dealing with unidentical agents." Even if "man units" were available, he doubted whether these could be used interchangeably, since the amount of the drug required to initially digitalize a patient would be different from that required to maintain him, for various types of digitalis. For example, when a rapidly dissipated drug, such as strophanthin, was used, a larger percentage of the initial digitalizing dose would be required for maintenance therapy than when digitoxin was used.

DeGraff[52] agreed that "the only purpose of a biological assay is to give us some indication of the possible potency in man," but that all digitalis "should be checked on man, . . . particularly if the digitalis contains an unusually large amount of a slowly eliminated fraction."

In 1946, Gold[103] reviewed the problem and advocated using human assay, since it seemed to him "the only present remedy to the problem of securing uniformity of digitalis preparations for oral administration in man."

In conclusion, it appears obvious that despite many years of intensive efforts to develop a reliable biologic assay method for digitalis, new preparations must be tested clinically in order to establish their effectiveness in man.

two distinct categories. The first group is comprised of ambulatory patients who require digitalis alone, or an occasional mercurial diuretic or minor restriction of salt to control all signs and symptoms of congestive heart failure. The second group consists of patients whose cardiac status is such as to warrant the maximum use of digitalis, adjuvant therapy with diuretics, controlled intake of sodium, and moderate to marked limitation of activity. According to the excellent study of Gold and DeGraff,[129] the first group is known to need smaller quantities of digitalis than the second group, in order to remain compensated. Wyckoff, Gold and Travell,[130] and Gold and DeGraff[129] noted that patients in the first group had "a wide margin between the amount of the drug necessary to produce full therapeutic effects and the maximum amount that can be tolerated without toxic symptoms." Indeed, it is frequently noted that patients in this class receive far more digitalis than they require, and are poor subjects for clinical evaluation.[129-131]

It is common experience that wide latitudes in compensation, frequently unassociated with symptoms, exist in ambulatory cardiac patients. Wyckoff, Gold and Travell[130] proved this when testing two unknown digitalis preparations. They found that an erroneous statement in regard to potency would have passed undetected had only small doses been used, and that only when large doses were employed was the error disclosed in the form of toxic symptoms. These patient can tolerate much larger doses of digitalis than are necessary to maintain a condition of optimum improvement. Because of this wide therapeutic range, "moderate differences in biological activity of digitalis escape notice in clinical practice."

On the other hand, the second group of patients has a very narrow therapeutic range. The quantity of digitalis necessary to produce toxicity over and above that having a therapeutic effect is very small.[113] We specifically have chosen to use these patients, since there is absolutely no question as to the minimum therapeutic dosage necessary to maintain compensation. We believe that it is only with this type of patient, in whom the therapeutic dose approaches the toxic one, that a digitalis preparation which might produce a greater therapeutic response without toxicity might be demonstrable. Minor fluctuations in the cardiac status of patients with advanced failure, in contrast to those with a mild condition, are more readily apparent to both patient and physician.

In the clinical evaluation of digitalis we have been impressed with the necessity for maximal standardization of conditions. We believe that broad groupings of large numbers of cases for statistical purposes is not valid with reference to human assay, since the individual variability of cardiac patients is so marked.

Our study was concerned with the clinical assay of several digitalis preparations in hospitalized patients. In addition, we have applied our method to the evaluation of gitalin. This preparation was introduced into clinical use by Batterman and associates,[113] as a cardioactive glycosidal derivative which exhibits a remarkably wide range of dosage between toxic and therapeutic levels Because the patients of this group resist all efforts to restore adequate compensation, the merits claimed for gitalin would be of obvious clinical importance.

Technique. Thirteen patients were carefully chosen from the wards of the hospital (Table I). All of these patients had been under constant observation for many months, and, of necessity, in all at least one digitalis preparation had been raised to a toxic level in an effort to increase the therapeutic response. All patients were on a fixed low-sodium diet, which was not altered during the period of observation. All but 2 patients required frequent injections of mercurial diuretics to control manifest edema or symptoms associated with the retention of fluid The diuretic dose was not altered during the study, except when necessary to relieve congestive failure. Physical activity was limited markedly in this group, and was not altered during study. If adjuvant therapeutic agents were in use, such as ammonium chloride, xanthines, and oral diuretics, these were continued on a fixed dosage schedule. It was believed that any change in the cardiac status of these patients would be readily demonstrable, and could be directly at-

should have produced toxicity in 65 per cent of the patients. It is difficult to accept this obvious discrepancy which appears to contradict the previous claims for gitalin, since this interpretation is based upon their published data.

Hejtmancik and Herrmann,[120] reporting on the clinical use of gitalin in 135 patients, were unable to establish equivalent potency, although they reported that the maintenance dose was 59 per cent of the toxic dose in 22 patients. They concluded that the drug was superior when substituted in a group of refractory patients, but a review of the records indicates that the patients lost their signs of toxicity with equivalent dosage.

In 1953, Luisada and Haring[121] reported that gitalin was the drug of choice, on the basis of electrocardiographic studies, but they could not account for their results in a subsequent paper.[122]

Dimitroff and co-workers[123] were enthusiastic about the drug after clinical trial in 68 patients, although a review of their data disclosed that only 8 patients appeared to do well. However, once again equivalent quantities were used and the loss of toxicity was the basis for their conclusions. In addition, the maximum tolerated dose of digitalis was not carefully established prior to substitution by gitalin.

In 1955, Dyke[124] noted that when gitalin was substituted for digitoxin in patients with auricular fibrillation a rise in the ventricular rate occurred after atropine. This observation, which was the first critical one, was lost among several other enthusiastic reports.[125,126]

In 1957, Bryfogle and his group[127] attempted to re-evaluate gitalin in 37 patients with auricular fibrillation. In 13 cases the authors were able to report on the therapeutic as well as toxic effects. They found that .5 mg. of gitalin was equivalent to .1 Gm. of digitalis leaf. They could not substantiate decreased toxicity nor wider therapeutic range.

The most recent review of this controversial subject was made in 1960, by Fleisher and Linde,[128] who maintained that no conclusive evidence had been published to substantiate or disprove the claims for gitalin, and that further study was needed.

General considerations

At present a large number of digitalis preparations is available to the practitioner. We have titrated several preparations in a select group of cardiac patients. From this experience we believe that in any human assay of digitalis the patient used in the investigation as well as the criteria used for evaluating the drug frequently have a marked influence on the results obtained. Regardless of claims of specific superiority for one preparation over another, the physician is only interested in using the drug which does the most for his cardiac patient in terms of improved myocardial efficiency.

Although it is generally agreed that animal assay has, at most, a limited value, as yet no uniform method of human assay has received widespread acceptance. The problem of determining the therapeutic efficacy of each digitalis preparation remains a dynamic one. In the comparison of the effect of an unknown preparation with that of a known standard, certain schemata have been proposed, and some of these have proved to be most valuable. The effect of digitalis on the ventricular rate of patients with auricular fibrillation is an example of this. Unfortunately, this technique cannot be used on patients with regular sinus rhythm, since congestive failure may be relieved without a change in heart rate. Parenthetically, a rare patient with auricular fibrillation will have complete restoration without alteration of his tachycardia.

In general, we believe that the estimation of digitalis dosage according to heart rate is unreliable. One can say that each patient has an optimum heart rate at which the heart muscle is most efficient. If adequate digitalis is given to attain the maximum efficiency of muscular contraction, the heart rate will adjust itself according to the basic demands made upon it. Consequently, clinical comparisons based solely upon changes in the heart rate are open to wide variations, unless very large numbers of patients are investigated. Our experience in utilizing the electrocardiogram as an accurate method for titration in human beings has been totally unsatisfactory.

For purposes of clarification, it is convenient to classify cardiac patients into

Mercurial dosage per week (c.c.)	*Digoxin (mg.)*	*Days*	*Results**	*Gitalin (mg.)*	*Days*	*Results**
				.25	3	+++
6	.5	31	M.F.	5	24	+
	625	2	Toxic	625	10	Toxic
8	625	60	+++			
	75	120	++	.75	5	+++
	1 0	34	+	1.0	11	++
	1 125	22	M.F.			
	1 25	3	Toxic	1.25	27	M.F.
				1 5	8	Toxic
Oral+2	25	9	+++	.25	10	++++
	.375	44	M.F.			
	.5	10	Toxic	5	45	M.F.
				.625	10	Toxic
2	.25	450	M.F.	25	40	++
				.375	32	M.F.
				5	8	Toxic
4	.25	39	M.F.			
	.375	17	Toxic			
				.5	51	Toxic
	.5	15	M F.			
	.625	12	Toxic	625	43	M.F.
				75	21	Toxic
4	.75	24	++			
	825	67	M.F.	825	6	+++
	1 0	4	Toxic	1 0	33	M F.
				1 25	4	Toxic
8	43	44	M.F.			
	.5	14	Toxic	5	6	++++
				.625	6	Toxic
4	75	27	M F.	75	12	+++
	1 0	90	Toxic	1 0	6	++
				1 125	21	+
				1 25	23	Toxic
6	5	69	++			
	625	32	M F.			
	75	6	Toxic	75	5	+++
				875	8	Toxic
2	5	56	M F.	5	15	++
	625	20	Toxic	625	9	+
				75	23	M.F.
10	.5	27	+	.5	8	++++
	625	35	M F.			
	75	20	Toxic	75	30	+
				825	25	Toxic
7	.25	28	M F.			
	.375	6	Toxic			
				5	39	+
				.625	10	Toxic

MF. Myocardial fibrosis. AI: Aortic insufficiency. AS. Aortic stenosis. TI: Tricuspid insufficiency. TS: Tricuspid stenosis. AF: Auricular
MI. Mitral insufficiency.

Table I

Patient	Age (yr.)	Cardiac diagnosis	CHF (yr.)	Duration of therapy (yr.)	
				Digitalis	Mercurials
E.L.	66	ASHD, HCVD, EH, CS, MF, AF	9	7	4
J.W.	57	Syphilitic EH, AI, AF, RSR	2	2	2
M.R.	53	RHD, EH, MI, MS, AI, AS, AF	6	4	1
J.B.	56	Syphilitic AI, aortic aneurysm, EH, RSR, angina pectoris	2	2	2
C.M.	57	Syphilitic AI, EH, RSR	3	1	1
J.D.	37	RHD, EH, MI, MS, AF	3	1	0
J.A.	60	Syphilitic ASHD, EH, AI, RSR	1	1	1
S.G.	63	RHD, ASHD, EH, CS, MF, MI, MS, RSR, angina, healed infarct	1	1	1
L.S.	50	Syphilitic EH, AI, aortic aneurysm, RSR	1	1	1
W.M.	63	HCVD, ASHD, EH, RSR	3	1	1
V.P.	22	RHD, EH, MI, MS, AF	4	4	1
M.B.	42	RHD, EH, MI, MS, AI, AS, TI, TS, AF	4	4	4
C.S.	76	HCVD, ASHD, EH, CS, MF, AF	4	4	3

*M.F.: Minimal failure. Plus signs indicate the degree of heart failure.
ASHD: Arteriosclerotic heart disease. HCVD: Hypertensive cardiovascular disease. EH: Enlarged heart. CS: Coronary sclerosis. [illegible] fibrillation. RSR: Regular sinus rhythm. CHF: Congestive heart failure. RHD: Rheumatic heart disease. MS: Mitral stenosis.

to be due to digitalis. All clinical changes in rhythm were confirmed by electrocardiogram.

We did not determine the minimal therapeutic dose of digitalis in this group of patients, since all of them required other therapy as well as the maximum use of digitalis. Therefore, we ascertained the maximal tolerated dose and the toxic dose of the preparations tested in most of the patients. Two drugs, digoxin and gitalin, were investigated most extensively. In these patients we found gitalin to be as convenient as digoxin for maintenance therapy. Toxicity due to gitalin tended to last somewhat longer than that due to digoxin, and there was some delay in the onset of full therapeutic effect. The most striking observation was the sensitivity of the technique in demonstrating extremely small variations in the potency of digitalis. The maximal tolerated dose for both drugs was determined in 10 patients, and the toxic dose in 11 (Table II). Reproducible clinical changes were consistently observed with increment changes of .125 mg. for both drugs.

Gitalin had been reported to be as potent, milligram per milligram, as digoxin.[18,19] However, we found that all but one patient required from 10 to 50 per cent more gitalin to obtain comparable control. The average for all of the patients was 30 per cent. This slight difference, which is readily apparent in these patients in whom the toxic and maximal tolerated doses are almost identical, would probably have been overlooked if patients with a mild cardiac condition had been used in the experiment. It is interesting that the average of the individual ratios for the toxic doses of digoxin and gitalin fell within a comparable ratio of .72 (Table II).

In other words, gitalin, on a weight basis, appears to be approximately 30 per cent less potent than digoxin. All previous techniques for the evaluation of the potency of digitalis have been insensitive to this difference. This is comprehensible when one realizes that this difference would be equivalent to reducing the total digitalis of a patient receiving 0.1 Gm. of digitalis leaf daily to 0.5 Gm. weekly. It would be most unusual for an ambulatory cardiac patient to lapse into failure with this insignificant reduction in digitalis. On the other hand, investigators who have utilized toxicity studies in assays would be misled by the results which can be predicted from this small difference in potency. Our data appear to indicate that doubling a presumable equivalent dose of the two drugs would, in reality, be giving about 60 per cent less gitalin.

It will be necessary to apply this technique to many patients with various kinds of heart disease in order to establish statistical proof of this approach to digitalis bioassay. However, if the theory is validated, it is conceivable that only a few well-controlled patients would be required in order to assay any new digitalis preparation as one used to assay crude liver for the treatment of pernicious anemia.

Summary

The bioassay of digitalis is reviewed, and a rational approach to the evaluation of digitalis based upon individual clinical patient data is recommended as the most satisfactory and accurate method for titration of digitalis. Utilizing the proposed technique, we studied gitalin in a small group of 13 hospitalized patients with heart disease of varied etiology. It was found that gitalin produced no improvement in clinical status with maximum dosage. Gitalin was found to be approximately 70 per cent as potent as digoxin on an equivalent weight basis in this limited study. These findings conflict with published data on the preparation. It would appear that these preliminary observations warrant further study with regard to human bioassay of digitalis preparations.

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Table II

Patient	Maximum tolerated doses (mg.)		Therapeutic ratio of digoxin to gitalin	Toxic doses (mg.)		Toxic ratio of digoxin to gitalin
	Digoxin	Gitalin		Digoxin	Gitalin	
E. L.	5	5	1 0	625	.625	1.0
J. W	1 125	1 25	90	1 25	1 5	0.83
M. R.	375	5	0 75	5	.625	0 80
J B.	25	375	67	5		
C M.	25			375	5	75
J D.	5	625	80	625	75	84
J A	875	1 0	88	1 0	1 25	80
S G	43	5	86	5	625	80
L. S	75	1 125	67	1 0	1 25	80
W M	625	75	84	75	875	86
V. P.	5	625	80	625		
M B	625	75	84	75	875	86
C S	25	5	50	375	625	60
Average			71			72

tributed to a variation in the cardiotonic activity of the digitalis used. Although several drugs were used (digitalis leaf, digitoxin, ouabain, digoxin, Cedilanid, and gitalin), all of the patients did not receive each drug. Since all these patients required maximal digitalis dosage, we found it most convenient to treat them with digoxin. The chief reasons for this choice were rapidity of the drug's action, the fractional dosage available, and the more rapid disappearance of toxic symptoms when they occurred. Digitalis leaf and digitoxin do not possess all of these advantages. Cedilanid does not lend itself to convenient maintenance therapy by mouth.

Gitalin was substituted in an amount lower than, or equal to, that represented as the equivalent potency for the medication which the patient was currently receiving. An attempt to maintain the patient on this fixed daily amount for a minimum of 3 weeks was made before increasing the dose, unless severe uncontrollable congestive failure ensued. After 3 weeks, if neither improvement nor toxicity occurred, the total daily dosage was raised by the smallest quantity of the drug size available: digoxin, 0.125 mg. daily; gitalin, .25 mg. every second day; digitalis leaf, 0.1 Gm. weekly; and digitoxin, 0.1 mg. weekly. The patient was then maintained on the same regimen for another 3 weeks. The process was continued until toxicity occurred. Whenever toxicity was induced, the drug was discontinued until all symptoms and signs abated and was then reinstituted at the previously maximal tolerated dose. This was continued for a minimum of 6 weeks in most cases. When the toxic manifestations were other than cardiac, the dose that produced toxicity was reinstituted and the toxicity reproduced, before being reduced to the maximal tolerated dose. The accepted signs of overdigitalization were regarded as toxicity, namely, weakness, malaise, anorexia, nausea, vomiting, visual disturbances, neuralgias, and cardiac arrhythmias. Of the systemic toxicities produced, 91 per cent were associated with electrocardiographic abnormalities, coupling, multifocal ventricular premature contractions, and atrioventricular block. The therapeutic status of each patient was evaluated by daily interviews and examination. Daily records of body weight and mercurial requirements were maintained. Careful attention was paid to the ventricular rate of patients with auricular fibrillation. In this manner, we believed that an adequate trial of any single dose of digitalis was obtained. We thought that, by the technique of repetitive dosage, extracardiac toxicities were proved

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proach more intelligently the mechanism of rhythm and conduction disturbances in myocardial infarction in general.

Schematically, the coronary arteries may be considered as three trunks: the left anterior descending, the left circumflex, and the right coronary arteries. Variations, subdivisions, and other branches are not the appropriate subject for discussion here. These three trunks vary greatly in their lengths, however, and the significance of this is considered in each topographic group, as is the location of the special branches which supply the sinus node and A-V (atrioventricular) node. As will be discussed later, atrial arrhythmias usually are associated with coronary occlusions proximal to the origin of the sinus node artery, and heart block with occlusions proximal to the origin of the A-V node artery.

Topography of myocardial infarction

Anterior infarcts. Anterior myocardial infarctions are due to occlusion of the left anterior descending artery. They involve the left ventricular free wall near the interventricular septum, the anterior portion of the septum (leading to their common designation as *anteroseptal*), and a small variable adjacent portion of the free wall of the right ventricle (Fig. 1). The size of the infarct depends among other things on the point of occlusion of the artery: larger infarcts follow more proximally located occlusions. It also depends on the number and proximity of unoccluded arteries in the adjacent free ventricular walls,[2] which in great measure determine the potential efficiency of collateral circulation. Finally, it depends on the length of the anterior descending artery itself, which virtually always not only reaches the cardiac apex, but also ascends 2 to 5 cm. up the posterior interventricular sulcus.

For the purpose of the present discussion it is especially important to realize that the left anterior descending artery in man virtually never supplies the sinus node or A-V node. Partly because of this, supraventricular arrhythmias and heart block are uncommon in anterior infarction. When they occur in anterior infarction, it is almost certain evidence that there is a second occlusion (old or new) involving one or both of the other two coronary trunks.[3] These considerations are modified when there is excess vagal discharge, overdosage with certain drugs, such as digitalis, associated presence of myocarditis, or any other factor which may introduce secondary (although clinically important) mechanisms.

There is no special predisposition to, nor unusual feature of, ventricular arrhythmias in anterior myocardial infarction. As long as there is a normal sinus pacemaker, however, it is more likely that orderly depolarization of the ventricles will prevail. Loss of normal sinus pacemaking, as during sinus arrest or complete heart block, is rare in anterior myocardial infarction, therefore, it may be anticipated that ventricular arrhythmias will be encountered more frequently with those infarcts (lateral and posterior infarcts) in which loss of normal sinus pacemaking is more often found.

Bundle branch block is not a clinical problem during acute myocardial infarction. With anterior infarcts which involve a large mass of septum, left bundle branch block and, more rarely, right bundle branch block can occur. Parietal or arborization blocks are sometimes difficult to differentiate from bundle branch block; the similarity of parietal block in posterior infarcts to right bundle branch block is an example of this.

Since the salient aspects of ventricular arrhythmias and bundle branch block as they pertain to this review are presented above in relation to all three groups of infarcts, they will not be repeated in the discussion of lateral and posterior infarction.

Lateral infarcts. Lateral infarctions are usually due to occlusion of the left circumflex artery, which most often terminates along the margo obtusus (Fig. 2). They do not involve the interventricular septum. When the marginal branch is long, it may reach the left ventricular apex, and its occlusion then produces a larger infarction. More commonly, however, the apical region of the margo obtusus is supplied by terminal branches of the left anterior descending artery. Most lateral infarcts are, therefore, in the

Fundamentals of clinical cardiology

Arrhythmias and conduction disturbances in acute myocardial infarction

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In acute myocardial infarction there are usually few complications, and care of the patient has become not only straightforward but somewhat stereotyped. Among the more serious complications which may occur are disturbances in the orderly electrical mechanisms of the heart. These are of particular importance because they so often are the basis for still other complications, such as shock or acute congestive failure.

Since optimal therapy must include preparedness for complications, it is necessary to be familiar with the pathogenesis of rhythm and conduction disturbances during acute myocardial infarction. Many factors which lead to heart block also predispose to arrhythmias, so that a rigid separation of their discussion can be misleading. The interrelationship of heart block and arrhythmias can be dealt with clearly through a topographic classification of myocardial infarctions.

There are several methods of classifying myocardial infarctions according to their location, and each method has its shortcomings. Electrocardiographic classification is the most familiar, but in this the terms "anterior" and "posterior" deal primarily with the position of the exploring electrodes and their presumed relation to actual cardiac surfaces. An example of the anatomic inaccuracy of this method is the general knowledge that "posterior" infarcts really involve the inferior or diaphragmatic surface of the heart. In favor of this method of classification, however, is its familiarity to virtually everyone, and the fact that the anatomic inaccuracies it conveys are generally recognized.

One of the most intriguing classifications, and possibly the most elegant anatomically, is that proposed according to muscle bundles involved.[1] Against this method is the general unfamiliarity with the anatomy of these myocardial bundles, their variability in different hearts, the difficulty in dissecting or otherwise demonstrating them, and the still incomplete knowledge of their blood supply.

For the purpose of this review, myocardial infarctions will be divided into three simple groups: anterior, posterior (diaphragmatic), and lateral. For each group the pertinent anatomy of the regional coronary arteries, and the major variations in size and location of the infarct will be presented. Particular emphasis will be placed on disturbances of rhythm and conduction usually associated with infarcts in each group. Although discretely localized infarcts are admittedly uncommon, and lamellar or patchy necrosis is more frequent, an understanding of the pathologic electrophysiology of infarcts in these three fundamental groups permits one to ap-

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and heart block is a much more common complication, because of involvement of the A-V node (Fig. 4). Furthermore, ischemia of the A-V node predisposes to atrial arrhythmias,[3,5] especially if the occlusion is also proximal to a sinus node artery arising from the left side.

Posterior infarcts. From the standpoint of disturbances in rhythm and conduction, posterior infarctions are the most treacherous infarcts, and are probably the ones which most often end in sudden death. The principal reason for this is the involvement of the A-V node. In 90 per cent of human beings the region of "pure" posterior infarction is supplied by the right coronary artery (Figs. 5 and 6), but, as indicated previously, exceptions are three times as common in men as in women.

When the right coronary artery extends to the margo obtusus, as it occasionally does, its occlusion not only produces an infarct at the crux but also in a large portion of the posterior left ventricular free wall (Fig. 6). Similarly, when its posterior descending ramus extends all the way to the apex, as it occasionally does, the subsequent infarct extends the same way. Since the right coronary artery rarely supplies much of the interventricular septum, with the critical exception of the A-V node and the area near it, most of the septum is spared in posterior infarction.

It has been observed that atrial arrhythmias during myocardial infarction are usually associated with an occlusion proximal to the arteries which supply both the sinus node and the A-V node.[3] For a

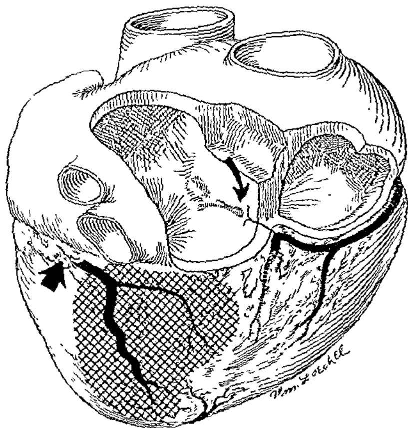


Fig. 2. Topography of a lateral myocardial infarction (see also Figs. 3, 4, and 6). Here occlusion of the distal portion of the left circumflex artery (*straight black arrow*) produces infarction in the upper half of the margo obtusus, but spares the crux of the heart and A-V node (*curved black arrow*), which are supplied by the right coronary artery. Infarctions of this type are manifest by primary electrocardiographic changes in Leads I, aV_L, V_6, and high V_{5-6}.

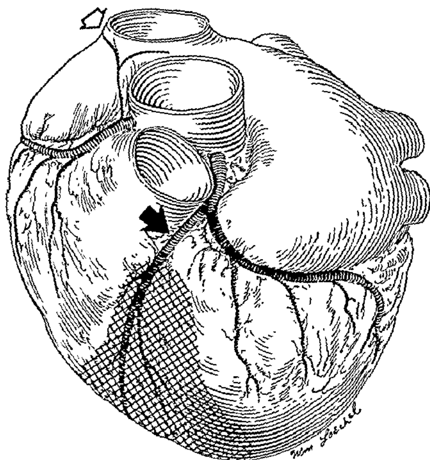


Fig. 1. Topography of an anterior myocardial infarction. A common site of the responsible occlusion in the left anterior descending artery is indicated by the black arrow. For orientation in this and subsequent drawings, the course and location of the sinus node artery arising from the right is shown, with the sinus node indicated by the white arrow. Here and in subsequent drawings, infarctions due to occlusion of a left coronary artery are indicated by cross-hatching, and those due to occlusion of a right coronary artery are indicated by a dotted area. Anterior myocardial infarctions are usually manifest in the electrocardiogram with diagnostic primary QRS and T-wave changes in Leads I, aV_L, and V_3-V_5.

wall near the atrioventricular sulcus, which has led to their frequent designation as "high" lateral infarctions.

Unlike the anterior descending branch, the left circumflex artery often supplies the artery to the sinus node and occasionally the one to the A-V node. For an occlusion to be proximal to the sinus node artery when the latter arises from the left circumflex artery, the occlusion must occur very near the main left coronary artery, since the sinus node branch in these hearts arises within the first few millimeters of the left circumflex artery (Fig. 3). Extension of this type of occlusion into the main left coronary trunk probably accounts for the very high mortality associated with atrial fibrillation during lateral infarctions.[4]

Although the left circumflex artery in man usually terminates at or near the margo obtusus, it occasionally extends in the atrioventricular sulcus to the crux of the heart and supplies the A-V node. This variation occurs in about 10 per cent of human beings, and is three times as common in men as in women. An occlusion of this type of left circumflex artery has two special characteristics: the resulting infarct is much larger, involving the posterior as well as lateral wall of the left ventricle,

physiologic[12] and anatomic[13] evidence for a normal dual conduction system in the human A-V node, one may expect that, during posterior myocardial infarction, nodal conduction may become either accelerated or delayed by either functional (vagotonia, transient ischemia) or morphologic (infarction) factors.

Atrial infarcts. As an epilogue to the topography of infarctions, brief separate consideration should be given to the atria. Atrial infarction has held a unique fascination for many serious students of cardiac electrophysiology, and its consideration is a standard gambit of the sophisticated clinical electrocardiographer. Although atrial infarcts may rarely lead to atrial rupture or formation of aneurysms, their clinical significance lies most clearly in their involvement of the sinus node.[3] Whether sustained atrial arrhythmias will follow the infarction of atrial myocardium which does not include the sinus node is uncertain, but there are a number of reasons why atrial infarction which *includes* the sinus node predisposes to such arrhythmias.[3,5]

Infarction of the sinus node impairs the normal dominance of the pacemaker. If the infarction of the node is complete, no impulse will be generated. It it is incomplete, a feeble impulse may be generated, but its delivery may be impaired. An observation which particularly suggests such a block or deviation of normal delivery of the sinus impulse is the peculiar

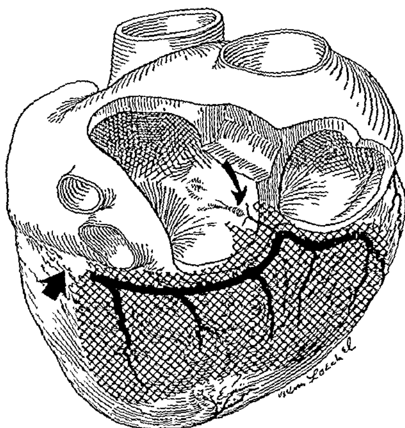


Fig 4. Topography of a large posterior and lateral infarction due to occlusion of a long left circumflex artery at the point indicated by the straight black arrow. This type of coronary distribution is unusual, occurring in only about 10 per cent of human beings; the much more common posterior infarction is shown in Fig. 5. Here the A-V node (*curved arrow*) is involved and heart block is to be anticipated during the acute infarction. Primary electrocardiographic changes occur in Leads III, aV_F, V_{6-8}, and high V_{3-5}; significant but lesser changes may also appear in Leads I and aV_L.

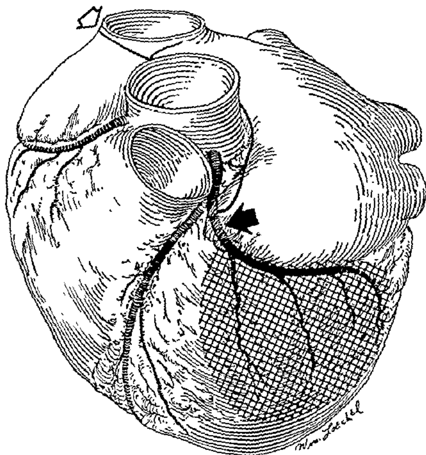


Fig. 3. Topography of a more anteriorly located lateral myocardial infarction. The left circumflex artery here is shorter than that shown in Fig. 2 and corresponds to the type also shown in Fig. 6 Occlusion at the point indicated by the black arrow causes the infarction shown, sparing the blood supply to both the sinus node and the A-V node. Any proximal extension of such a thrombus may lead to atrial arrhythmias by blocking the sinus node artery (*sinus node is indicated by the white arrow*), but may also lead to complete occlusion of the main left coronary artery (*see text*). The primary electrocardiographic changes are in Leads I, aV_L, and high V_{1-4}.

single occlusion to be proximal to both these nodal arteries, it almost has to be in the proximal right coronary artery (Table I). It must be remembered, however, that multiple occlusions are the more common finding in fatal myocardial infarcts.[6,7]

Several anatomic reasons have been given for anticipating that atrial (and ventricular) arrhythmias and heart block should be more common with posterior infarcts. Another predisposition to disturbances of cardiac electrical mechanisms which is commonly manifest in patients with these infarcts is an inordinately severe vagotonia.[8,9] The basis for such excess vagal discharge has previously been obscure, but the recent observation by Juhasz-Nagy and Szentivanyi[10] of vagal neuroreceptors in the region of the coronary sinus may be the explanation for this clinical observation in man.

How infarction of the A-V node may lead to heart block is readily apparent. In addition, ischemia of this node may paradoxically lead to accelerated conduction.[11] Such acceleration may cause preexcitation and the appearance of false bundle branch block, but, of more clinical significance, it may lead to reciprocal rhythm and paroxysmal supraventricular tachycardia. Since there now is both

probably infarction of the sinus node and, usually, ischemia or infarction of the A-V node also.

There is little question that sustained heart block from acute myocardial infarction is due to structural damage of the A-V node or the bundle of His. Heart block during acute infarction is more often not sustained, however, and one important reason may be that it can be quickly fatal. For example, transient A-V block during acute severe myocardial ischemia, a period of maximal ventricular irritability, must predispose to a disorganized and lethal ventricular rhythm. Thus, almost by definition, heart block during acute myocardial infarction will usually be either lethal or transient. Some of the same contributory factors which predispose to atrial arrhythmias also predispose to transient heart block.

In the order of their probable importance these contributory factors include vagal and vagomimetic reflexes, excess circulating catecholamines, and hypercalcemia. The basis for considering the latter is the most tenuous and requires further study Calcium has a vagomimetic effect, patients with myocardial infarction are usually immobilized, and ionizable calcium has

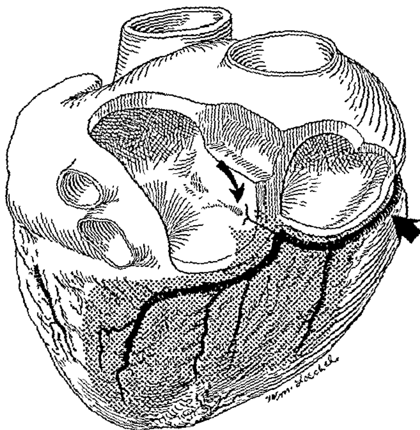


Fig. 6. Topography of a large posterior and lateral infarction due to occlusion of a long right coronary artery at the point indicated by the straight black arrow. Note the similarity of the infarct to that shown in Fig. 4. This coronary distribution is also uncommon, occurring in about 20 per cent of human beings. The A-V node (*curved black arrow*) is involved and heart block is to be anticipated. In this and preceding illustrations the more proximal occlusion of either the right or left coronary artery may occur upstream from the origin of the sinus node artery (*shown in its typical right and left origin in Figs. 1 and 3, respectively*), and then be associated with atrial arrhythmias. Possible combinations are indicated in Table I. In the infarct shown here the primary electrocardiographic changes appear the same as for the one seen in Fig. 4.

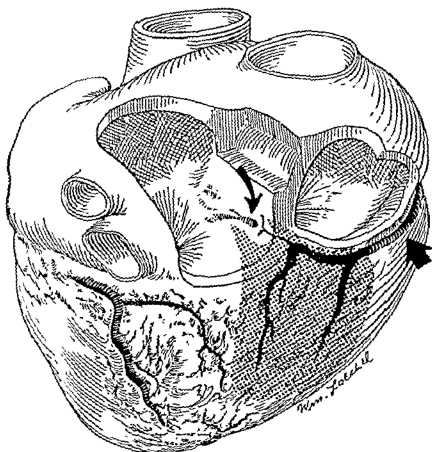


Fig. 5. Topography of the most common type of posterior infarction, due to occlusion of the right coronary artery (*straight black arrow*). Note that the volume of ventricular myocardium infarcted is not large. The A-V node (*curved black arrow*) is involved, however, and heart block is to be anticipated. This distribution of the right coronary artery occurs in about 70 per cent of human beings. Primary electrocardiographic changes with such an infarct appear in Leads III, aV$_F$, and V$_1$. Esophageal leads may be necessary to demonstrate conclusive changes.

localization of some sinus node infarcts at the junction of the node and atrium.[3]

The great majority of atrial infarctions due to coronary disease are in the right atrium.[11] This is hardly surprising since the largest atrial artery is the one which supplies the sinus node,[7,15] and the sinus node is in the right atrium. Although there are occasionally exceptions, most of the other atrial arteries are, by comparison, much smaller. Whether atrial myocardium will infarct if flow in the sinus node artery (which normally supplies significant portions of both atria) remains normal is uncertain, but such infarctions may be expected to be considerably smaller than ones associated with coronary occlusion proximal to this artery. More important, however, is the probability that most atrial infarcts of any appreciable size *will be* associated with involvement of the sinus node.

Contributory factors

An attempt to reproduce atrial arrhythmias during myocardial infarction experimentally demonstrated that many contributing factors are involved, and the exact nodal histopathology found in man under these circumstances was not reproduced.[8] The probable reason that the histopathology was not reproduced is that these were acute experiments which lasted a few hours, whereas the situation in man is one which lasts for days or weeks. Whatever the other factors involved are, the major basis for sustained atrial arrhythmias from myocardial infarction *in man* is

fication that acute posterior infarctions are the most dangerous in regard to the likelihood of sudden death due to serious disturbances of cardiac rhythm or conduction. As a corollary, mortality in the acute phase of acute posterior infarction is probably much higher than present statistics suggest. Most such statistics fail to include the patients who died in the emergency room or at home or on the street, which is where the patient with abrupt fatal disturbance in cardiac rhythm or conduction is most likely to die. As evidence of the ubiquity of transient heart block or asystole in patients with acute posterior infarctions who survive to reach the hospital, it is impressive how many of them on careful questioning give a history of syncope. Some are hospitalized unconscious. Many have had extensive negative neurological studies in the past.

Because posterior infarcts usually involve the A-V node, drugs which may further depress A-V conduction should be avoided or used with proper caution in these patients. The prophylactic use of quinidine is of questionable value in any acute myocardial infarction, but quinidine carries with it a particular hazard in the patient with acute posterior infarction. Digitalis also has a vagomimetic effect, slowing A-V conduction. Both digitalis and quinidine should still be employed if the indication is clear, but the indications should be carefully considered.

There is no more effective medication for the pain of acute myocardial infarction than morphine. Its vagomimetic effect is well known, however, and this may have undesirable cardiac effects. A suitable remedy for this problem is simply to employ atropine with every dose of morphine. This not only abolishes the vagomimetic effect of the morphine, but with this combination of drugs there is no clinically manifest vagolytic effect by the atropine. The conventional dose of 1/4 grain of morphine for 1/150 grain of atropine is a satisfactory combination for this purpose.

Since the natural history of most arrhythmias and conduction disturbances in myocardial infarction indicates that they are usually transient, this is important to remember in treatment. Against this reassuring point, however, is the danger that the nontransient disturbances may be fatal. The decision of how vigorously one must try to prevent such disturbances will vary with each patient, as does most intelligent treatment, but, in general, if the patient is doing well, one must weigh carefully the possible harm of many of the so-called "prophylactic" measures, such as the routine use of quinidine or hasty digitalization. If the patient with acute myocardial infarction develops atrial fibrillation with a slow ventricular response and no evidence of cardiac failure, how energetically should one attempt to restore sinus rhythm? If the atrial fibrillation in such a case is sustained, perhaps it is because the sinus node has been destroyed by infarction. It would be hollow triumph to abolish the fibrillation but have no sinus node to take over. Atrial fibrillation with a rapid ventricular response is, of course, a different question and should be treated with digitalization.

In deciding whether to treat an arrhythmia or heart block during acute myocardial infarction, one should remember that rapid ventricular rates are associated with a reduction in cardiac output, particularly when the damaged ventricular myocardium is partially noncontractile. The reduction in output under these circumstances is due to both decreased diastolic filling (shorter filling period and decreased ventricular distensibility[22]) and less efficient ventricular ejection because of some noncontractile myocardium. Slow heart rates usually associated with complete heart block reduce cardiac output in the following manner: with bradycardia in normal hearts, cardiac output is maintained by a marked increase in stroke volume, but with ischemic or infarcted myocardium the ventricle is limited in its ability to increase stroke volume, so that slower rates are, therefore, inevitably associated with a reduction in output.

Since reduced cardiac output may enhance the progression of myocardial ischemia to infarction,[23] or, by reducing the efficiency of collateral circulation, cause enlargement of an area of myocardial infarction, treatment of rapid ventricular rhythms or unusually slow ones becomes an important prophylactic consideration even in the absence of obvious clinical

Table I. Nodal artery origins in 106 human hearts[2]

A-V node artery from the right Sinus node artery from the right	44%
A-V node artery from the right Sinus node artery from the left	38%
A-V node artery from the left Sinus node artery from the right	8%
A-V node artery from the left Sinus node artery from the left	4%
Others	6%

been shown to increase slightly during even brief immobilization.[16] Whether this is an important factor during human myocardial infarction has not been determined.

During acute myocardial infarction the circulating cathecholamines become elevated,[17] and transient acute hypertension has been described.[18] The positive chronotropic effect of catecholamines may predispose to either atrial or ventricular arrhythmias. How often this is actually the case in man requires further study.

Certainly, the most important of these contributory factors are the vagal and vagomimetic reflexes. It has even been suggested by able clinicians that excess vagal discharge is the universal mechanism of sudden death during myocardial infarction.[19] There is abundant literature describing the profound effect on both sinus pacemaking and A-V conduction by vagal discharge. There is also good evidence that the effect of vagal discharge on repolarization in extranodal atrial myocardium may predispose to atrial fibrillation.[20] What is less clear is why and how excess vagal discharge occurs during acute myocardial infarction.

Much of this vagotonia is likely due to emotional and psychogenic response to an acute illness which is both extremely painful and overwhelmingly frightening. In addition to organic or somatic causes for fright, such as acute dyspnea due to pulmonary edema, there is every patient's awareness that something is gravely wrong with his heart and that he may die. The fact that responses of patients to such a situation differ was the basis for the classification of these responses by older clinicians as sympathicotonic and vagotonic. Richter[21] has now presented experimental evidence to suggest that in situations of hopelessness or despair the universal response may be vagotonic. Whether this is or is not generally applicable in man, there is little question that many individuals do have an emotional response which is primarily manifest as excess vagal discharge.

Equally intriguing as a possible source for a vagal reflex during acute myocardial infarction are the vagal neuroreceptors in the region of the ostium of the coronary sinus, which were recently reported.[10] This report did not discuss the A-V node in the study of these receptor sites, but the anatomic proximity of the node, which is only a few millimeters from the ostium of the coronary sinus,[15] would lead one to suspect that these neuroreceptors may equally relate to the node or perhaps exclusively to the node.

Whether or not these juxtanodal vagal neuroreceptors are in fact functionally related to the node, it is highly probable—simply from their anatomic location—that they are involved during posterior myocardial infarction, just as the node is (Figs. 4-6). This may be the explanation for the previously puzzling clinical observation of a high incidence of vagal symptoms during acute posterior myocardial infarction, such as intense sinus bradycardia, sialorrhea, tenesmus, nausea, vomiting, diaphoresis, and tracheal burning or spasm.[8,9]

Clinical management

Brief remarks here will be limited to aspects of treatment which pertain particularly to the mechanisms just discussed. The choice of drugs and other measures for the treatment of disturbances of rhythm or conduction has been the subject of numerous modern reviews as well as an appropriate topic in standard textbooks of cardiology. Emphasis here will be on pathogenesis of these disturbances as it applies to treatment.

It is apparent from a topographic classi-

Annotations

Vasoactive polypeptides

Within recent years various polypeptides with vasoactive properties have been discovered, and the isolation, identification, purification, structure, synthesis, and metabolism of many of them have been described. Furthermore, as a result of these investigations, several analogues of these peptides have been identified. Intensive study has been directed toward the polypeptides: kallidin I or bradykinin,[1-10] angiotensin I and II,[11-22] oxytocin, vasotocin, and the vasopressins,[23-31] kallidin II,[32,33] substance P,[34,35] peptide B,[36,37] and many others, including substance U,[38] pepsitocin,[39] and pepsitensin.[39]

The vasoactive polypeptides are either vasopressor or vasodepressor. The vasopressor polypeptides include angiotensin II and related peptides,[11,22,40] pepsitensin[39] and oxytocin, vasotocin, and the vasopressins.[23-31] Kallidin I or bradykinin,[1-10] kallidin II,[32,33] substance P,[34,35] substance U,[38] and peptide B,[36,37] formed from the reaction of bovine thrombin on bovine fibrinogen, are vasodepressors.

The relationship between the biologic activity and structure of these polypeptides has stimulated intense investigation. Conflicting reports have appeared for different biologically active polypeptides, with reference to the correlation between biologic properties and structural integrity. Guttmann and Boissonnas[41] have shown that the biologic activity of bradykinin may be completely or partially lost with even minor structural changes. The two terminal basic arginine moieties of bradykinin are a unique feature of this molecule, but basic amino acids in these positions do *not* insure biologic activity as reported by Vogler and associates,[42] who demonstrated absence of biologic activity for 1,9 bisdiaminobutyric acid bradykinin. In contrast, Woolley and associates[43,44] have reported that neither the amino acid sequence nor the exact amino acid composition in the peptide chain is essential for the biologic activity of bradykinin or strepogenin. Recent reports in regard to the structure and function of oxytocin and vasopressin have also yielded conflicting results.[23-31,45] Smeby and associates[19] have reported that a peptide must have at least six amino acids, a tyrosine in position 4, a proline in position 7, and a phenylalanine with a free carboxyl group in position 8, in order to have angiotensin II activity. As these observations indicate, it is likely that, although all of the relationships between the structure and function of these biologically active peptides have not been completely defined, there is a specific relationship between structure and biologic activity. The chain size, amino acid content and sequence, steric relationships and spatial conformation of the peptide are undoubtedly of varying degrees of importance in determining biologic activity.

The function of these vasoactive polypeptides in the control of homeostatic mechanisms of the vascular system under physiologic and pathologic conditions has stimulated both investigation and speculation.[18,20,33,46] Many investigations have been designed to characterize the mechanisms through which they regulate the blood pressure and to describe their rates of synthesis and degradation. The substrates of many of these vasoactive polypeptides may be found in the same serum globulin fraction, and it is interesting to note that the production of angiotensin II by incubation of this α-2-globulin fraction with renin prevents the elaboration of kallidin I or bradykinin by the subsequent reaction of the same α-2-globulin fraction with trypsin.[46] The formation of these biologically active polypeptides by the action of proteolytic enzymes on blood α-2-globulin is, therefore, a possible mechanism which contributes to the physiologic regulation of the blood pressure in man.

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evidence of cardiac insufficiency. In these as in other clinical dilemmas there are no pat rules for treatment, but a consideration of all the factors discussed above makes the individual decision for each patient a more rational one.

Finally, an understanding of the characteristics of these three groups of infarction permit certain prognostic considerations. The patient with anterior infarction may lose a large mass of myocardium and develop congestive failure but is less likely to develop acute emergencies due to rhythm or conduction disturbances. The patient with lateral infarction usually loses a smaller mass of myocardium but is more likely than the one with anterior infarction to have associated arrhythmias or heart block; when these occur, the prognosis with a lateral infarct is grave. The patient with posterior infarction is the one most likely to develop both heart block and arrhythmias, and his acute course is more likely to be suddenly fatal or stormy; since this infarct commonly involves a small mass of myocardium, however, the ultimate prognosis, once the acute phase is survived, is good.

Summary

From a consideration of cardiac anatomy and pathologic electrophysiology, acute myocardial infarctions may be classified into three groups: anterior, lateral, and posterior. Arrhythmias and conduction disturbances are least common in patients with anterior infarctions, and most common in those with posterior infarctions. A review of the mechanisms involved suggests that infarction of the sinus node or A-V node and excess vagal discharge are the most important pathogenetic factors. A brief discussion of clinical management is based on these considerations.

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Main cerebral artery disease as a cause of strokes

Until fairly recently, cerebral infarction has been ascribed to arterial thrombosis, and cerebral hemorrhage to arterial rupture. Despite early French observations in 1925[1] of the occurrence of cerebral infarction without thrombosis, this association was slow to achieve recognition. However, with the increasing use of cerebral angiography the concept of "cerebrovascular insufficiency"[2] on a basis of "caroticovertebral stenosis"[3] became widely accepted. This led to the introduction of reconstructive surgery designed to improve the flow of blood through narrowed or occluded arterial segments in patients with recurrent cerebral ischemic episodes. These operations are also frequently performed prophylactically in those who have already suffered permanent brain damage, to prevent their getting further infarcts.

As always happens in new fields, opinion swings widely from one extreme to the other, and we are seeing at present a return to the old idea of cerebral thrombosis as a prime cause of infarction. Careful observations[4] have shown a difference between old and recent infarcts. Although occlusion was demonstrable in only a minority of patients with long-standing cerebral infarcts, thrombus in the arteries of supply was found in 90 to 95 per cent of patients with acute brain softening. This raises the possibility that old infarcts may have been due to thrombosis of arteries which have later recanalized.

Has the time come to discard altogether the concept of "cerebrovascular insufficiency," with its emphasis on stenotic lesions of the larger vessels as a cause of cerebral infarction? It is unfortunate that most observations on the main cerebral arteries, particularly those in the neck, have been made in patients who died with strokes,[5] and little is known of the incidence of stenotic lesions of the large cerebral arteries in people with normal brains. This omission has been rectified recently[6] in an investigation which has shown almost as high an incidence of severe arterial stenosis in people with normal brains as in those with cerebral infarction. The authors of this latter paper suggested that much of the relationship between cerebral infarction and carotid-vertebral stenosis might be accounted for by age alone, since older patients have narrower arteries and suffer more frequently from cerebral infarction. Perhaps an infarct not caused by complete arterial occlusion needs for its production not only stenotic lesions of the arteries of supply, but also some other condition, such as heart disease, which causes a fall in blood pressure. Much evidence suggests that frank heart disease is present as often as not in cases of cerebral infarction.[7]

The relief of transient attacks of cerebral ischemia by reconstructive surgery cannot be taken to prove a pre-existing state of cerebrovascular insufficiency, because it is possible that operation removes a source of emboli. Some very interesting observations have recently been made of the retina in cases of internal carotid thrombosis, in which multiple small emboli were seen traveling along the retinal arteries.[8] Many of the attacks which formerly were considered to be due to spasm or to "cerebrovascular insufficiency" can now be more convincingly reinterpreted in terms of emboli passing to other parts of the internal carotid territory.

Turning to cerebral hemorrhage, we have witnessed a whole spectrum of different opinions during the last 20 years. Miller Fisher[9] supports the classic view that this condition is usually due to arterial rupture. However, many will remain unconvinced that simple spontaneous rupture is the whole explanation, especially since it is so difficult to rupture cerebral arteries by high intraluminal pressure,[10] and because, when the bleeding vessels can be found, they are often small. Welch[11] showed long ago that experimental intestinal infarction could be made

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Transfer of Cd^{115m} across the pericardium of dogs

The rates of transfer of radiocadmium, Cd^{115m}, across the intact pericardium of dogs were measured. This isotope was studied because of its many interesting features, and because it is an important and interesting trace element found in mammals, including man.[1-3] Cadmium is essential for certain enzyme functions.[4] Chronic cadmium-poisoning has been reported to produce cardiomegaly.[5,6] However, cadmium is not a useful experimental tool for the production of cardiomegaly, as originally anticipated.[7]

Cd^{115m} was instilled in the pericardial cavity in Ringer's solution in a concentration of approximately 5.5 mg. per 50 ml or 110 mg per liter, which is far greater than the concentrations normally found in mammalian tissues.[3] This concentration did not change the electrocardiogram. By methods and mathematical analyses previously described[8,9] the mean rate of transfer was 0.176 µg per square centimeter per minute; the range was 0.03 to 0.36 µg/cm²/min. This represents a daily bidirectional rate of transfer of about 150 mg. across the pericardium of the dog. Of the ions studied in this laboratory by this technique (D_2O, I^{131}, Cl^{36}, Na^{22}, Mg^{28}, Cd^{115m}),[8,9] Cd^{115m} had the slowest rate of transfer. This rate of disappearance of Cd^{115m} from the pericardial test fluid probably represents not only loss by transfer through the pericardium but also Cd^{115m} bound to protein and epithelial cells of the pericardium. Thus, like other serous membranes there is an extremely rapid transfer of many elements and complex substances across the pericardium. Because the pericardium is normally relatively dry in spite of the rapid and constant exchanging of fluid and electrolytes, the accumulation of fluid and solutes in pericardial diseases remains a great mystery.

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avascular or hemorrhagic at will, according to whether the arterial occlusion was complete or incomplete; and experimental embolic occlusion of a single leptomeningeal artery has been observed to produce hemorrhagic infarction in the gray matter.[12] It is interesting that massive cerebral hemorrhage has been produced in dogs simply by the readmission of blood to a brain made totally ischemic for a short time by increased intracranial pressure.[13] The fact that cerebral hemorrhage can be produced in this way, without the stress of hypertension, suggests that cerebral hemorrhage in man could be due to the readmission of blood into an area of infarction. Bleeding into the brain may be different in nature from bleeding into other organs because of the ease with which brain tissue can be disrupted. Thus, damage due to a small infarct might spread far beyond the original lesion. This hypothesis, by no means new, can be neither proved nor disproved without more evidence, but three corollaries of it are worth examining.

First, if cerebral hemorrhage and cerebral infarction share a common cause, the two conditions should often coexist. It is general knowledge that this is so; not only do we see areas of acute softening in cases of cerebral hemorrhage, but we also see long-standing cerebral cysts, presumably representing previously infarcted areas. In a personal series of 20 cases of cerebral hemorrhage, I observed coexistent cysts five times.[14]

Secondly, if hemorrhage is usually due to bleeding into an infarcted area, we should expect to find that the severity of stenotic vascular disease is as great in cerebral hemorrhage as in cerebral infarction. Yates and Hutchinson[5] found a high incidence of stenotic disease of the large arteries in cases of cerebral hemorrhage, but it was still not so great as in cases of cerebral infarction. However, their assessment was made by eye, and, when using a simple perfusion method of gauging the approximate caliber of the arteries at necropsy, my colleague and I were not able to find a significant difference between cases of cerebral hemorrhage and cases of cerebral infarction, although there was a clear-cut difference in the fluid-carrying capacity of these vessels in cases of strokes of all kinds, when compared with the vessels of people who died with normal brains.[14]

Thirdly, if cerebral hemorrhage is commonly due to bleeding into an area of previous infarction, we should not expect to find cerebral hemorrhage occurring in animals with experimental hypertension. Stamler[15] has made the statement, which I have not seen refuted, that massive cerebral hemorrhage, so commonly associated with high blood pressure in man, does not occur in benign experimental hypertension in animals. This suggests strongly that something more than high blood pressure is necessary for the production of cerebral hemorrhage.

Although arterial thrombosis clearly plays an important part in cerebral infarction, there is usually pre-existing stenotic vascular disease in addition. Possibly, the normally high blood pressure of nearly all such patients protects them against stagnation of blood in the brain. It is perhaps relevant that most cerebral infarcts occur during sleep, when the blood pressure is low. It is becoming fashionable to discount the significance of stenotic lesions of the main cerebral vessels in the neck. Certainly, collateral channels can be remarkably effective, as was shown by a recent report in which the cerebral blood flow of 2 patients with bilateral obstruction of the internal carotid artery was found to be normal.[16] It is often observed that there may be very little drop in pressure across a greatly narrowed segment of carotid artery. However, under average waking conditions, and under anesthesia, the systemic arterial pressure is considerably higher than it needs to be to perfuse the brain adequately. If we find a drop in pressure of, say, 2 mm. Hg across a narrow region of the carotid artery, this may be greater under different conditions, in which, at a lower blood pressure, the region itself is less distended, and the other main cerebral arteries are also less distended. The possibility of greater stenosis higher up the course of the artery must also be borne in mind. In additon, it is now well established that the vertebral, and sometimes the carotid arteries also may be partly or completely occluded during certain movements of the neck.[17] The hemodynamic significance of small lesions could be much increased in these circumstances.

There is a most urgent need to develop new techniques to study, during life, the resistance offered by various parts of the cerebral vascular tree under a variety of conditions. Until we have these new techniques, future discussion in this field will be increasingly sterile.

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pressures are inappropriate (strictly, the diastolic pressure occurs during the isometric phase of ventricular systole), these definitions are so deep-rooted that it would be unwise to introduce new terms. Accordingly, the expression "mean systolic pressure" should refer to the average of peak pressures which prevail over a period of time. To distinguish this from the average pressure that obtains in arteries *during* the period of ventricular ejection, the latter may be called "mean ejection pressure."

According to Rushmer,[14] the term "venous return" to the heart has been employed in many ways and requires a precise definition. In our opinion, a better term is "venous inflow," which is defined as the volume of blood that enters either ventricle over a period of time (usually a minute). At times, it may be distinguished from "venous return," which is the volume of blood that enters the atria over a period of time.

One could continue adding to this list, but the foregoing examples should serve to illustrate the point. It is earnestly hoped that this discussion will lead to prompt action by a group of investigators in the cardiovascular field to remedy the situation.

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A plea for standardization of definitions in cardiovascular functions

In 1950, a group of pulmonary physiologists[1] in the United States met to standardize their symbols and terms with the view of avoiding the confusion that existed in the English literature due to semantics. At present, there is a dire need for a similar agreement in the cardiovascular field, not so much on symbols as on definitions. To illustrate the state of confusion, the following terms might be considered.

The terms "hypoxia" (anoxia), "hypoxemia" (anoxemia), and "ischemia" are used synonymously by some authors. In general, when tissue cells do not consume sufficient oxygen to meet their *requirement under a given set of conditions*, they are said to be suffering from hypoxia (anoxia).[2,3] The term "hypoxemia" denotes a reduced oxygen *content* of arterial blood,[2] irrespective of the adequacy of the supply of oxygen to tissue cells. The low oxygen content *may be the result of low saturation of* hemoglobin (low pO_2) or low hemoglobin content of blood (anemia). Here, the importance of blood flow to the tissue must be borne in mind. Thus, a mild degree of hypoxemia may not result in hypoxia of a tissue if the blood flow and/or venous desaturation are proportionately increased. Some investigators[3,4] have used the term "hypoxia" to describe hypoxemia due to low arterial saturation. Berne, Blackmon, and Gardner[5] have used the term "hypoxia" for a reduction in the oxygen *content of tissue* rather than its oxygen *consumption*, presumably on the *assumption that the two decrease proportionately*. However, it is conceivable that under certain circumstances the oxygen content and oxygen consumption of a tissue may vary independently (e.g., hypothermia, cyanide poisoning), and, since there *are no methods* to quantitate tissue oxygen content, this concept of hypoxia does not seem to be a useful one. Some investigators[6] have used the term "anoxia" to describe arrest of blood flow (complete ischemia). This is not justified on the grounds that in complete ischemia, although anoxia is the most prominent disturbance, there are other derangements that may be functionally significant. In complete ischemia the tissue is deprived *of all* the nutrients that are brought by plasma (e.g., glucose, etc.), whereas in anoxia it is deprived *only of oxygen*. Besides, the metabolic products (CO_2, lactic acid, *etc.*) which are not washed away accumulate *to* very high concentrations. These other changes may contribute significantly to "wreck the biochemical machinery" of tissue cells. Hence, anoxia and ischemia are not synonymous.

Another example of confusion is the concept of "work" and "power" of the heart. External mechanical "work" as calculated conventionally by physiologists has always been expressed *per unit of time*, whereas in physics "work" does not involve time. For physicists, work per unit of time is "power." Some investigators[8] have complicated physiologic semantics by introducing the physicists' definition of "work" and "power." This is unfortunate *in that these physical definitions tend to aggravate* the confusion among physiologists, and, furthermore, the term "power" for a long time in physiology has been associated, somewhat loosely, with "force" of muscle contraction (be it in heart or skeletal muscle). According to Klip,[9] some authors[10] have also defined myocardial "power" as the quo*tient of diastolic aortic pressure* × blood volume in the left ventricle divided by duration of isometric contraction. Klip has pointed out that this is not physically justified because the energy needed to bring the left ventricular pressure up to the value which can open the aortic valves *is not equal to the* product of diastolic pressure in the aorta and the volume of blood in the left ventricle. In our opinion, one cannot speak of "power" during this period for the simple reason that practically no external "work" is done during the period of isometric contraction. The volume of intraventricular blood is practically *unchanged during this period.*

In view of these and other considerations, we believe that some of the terms used by physical scientists are not entirely appropriate in physiology. Nevertheless, a judicious selection of physical *definitions is highly desirable.*

The term "work capacity" of the heart has also been used in different ways. This is discussed in a separate communication.[11]

A further illustration of misleading terminology is related to the expression "mean or average systolic pressure" in arteries. Wiggers,[12] and Sarnoff and associates[13] have used this term for the mean pressure *during* the period of ventricular ejection. But conventionally, "systolic" pressure refers only to the momentary *peak* pressure during ejection. *Hence,* the term should refer more appropriately to the *average of peak pressures* which exist in the arteries over a period of time. Although the conventional definitions of "systolic" and "diastolic" arterial

to surgical relief. In the area of unilateral renal disease a good ground work is laid which can be supplemented from the recent literature in this rapidly moving field. The theory, action, and side effects of most of the drugs currently used are taken up, along with careful instructions in regard to their use. Guanethidine, a current favorite, is described, but sufficient experience for complete evaluation was lacking at the time of publication to do justice to this drug. The author side-steps the question of when to treat hypertension, and one is left to assume that he would treat all cases. A few words in regard to the order of trial of drugs and the drugs most useful in different types of hypertension would be desirable. The chapter on etiology and experimental hypertension is good and has an extensive, carefully selected bibliography.

This book will be useful to all physicians who must grapple with this problem and will be read with interest by those who specialize in this field.

DEVELOPMENT AND STRUCTURE OF THE CARDIOVASCULAR SYSTEM. An American College of Cardiology Monograph from *Cardiology—An Encyclopedia*. Edited by Aldo A. Luisada, M D., New York, 1961, McGraw-Hill Book Company, Inc , 225 pages. Price $9 95

This monograph consists of a collection of systematically arranged articles which pertain to the structure of the heart and blood vessels, each of which is written as a separate and more or less complete entity, independent of previously presented sections. For example, those who are interested in arterial vessels of the neck may study the four-page section on the aortic arch and its branches, wherein the principal innervations, anatomic variations, and anomalies are discussed and more than adequately illustrated. Similar presentations cover the pulmonary, renal, and hepatic circulations. The coronary circulation is incorporated in a section entitled "Arteries, Veins, and Lymphatic Vessels of the Heart." Of particular interest is the illustrative material, which consists of beautifully executed roentgenograms which were made after radiopaque injection of the human coronary arteries.

In general, all presentations are as complete as seems consistent with the objectives of this monograph. Special value lies in the bibliography, which consists of approximately 400 titles This is contained in a completely separate section, and is arranged alphabetically according to author. The index is adequate and arranged for the collection of cross-reference material

The opening chapter, "Embryology of the Heart and Major Vessels," contains descriptions which should be unusually clear to the uninitiated but is not so elaborately illustrated as subsequent chapters. Of special value is the section which deals with partitioning of the truncoconal segment and the embryogenesis of transposition defects and stenoses.

In view of the fact that this monograph deals with the structure and angioarchitecture of heart and blood vessels and contains special sections devoted to the macrocirculation and microcirculation of the lungs, liver, and kidneys, one wonders why a section devoted to the phylogeny of the cardiovascular system has been included, whereas the complex peculiarities of the cerebral circulation are omitted.

With this one exception, this monograph seems to be a useful and ready source of specific information and should "help anatomists and physicians in their difficult task as teachers and researchers."

VECTOR ELECTROCARDIOGRAPHY. By Herman N. Uhley, Assistant Chief, Department of Medicine, Mount Zion Hospital and Medical Center, San Francisco, Calif. Philadelphia, 1962, J. B. Lippincott Company, 339 pages.

This volume is not aimed at instructing the reader in the fine points of electrocardiography or vectorcardiography. In fact, there are no actual electrocardiograms and only one actual vectorcardiogram in the book. The aim is to present the relationship between the two, using a few frequently encountered electrocardiographic "syndromes."

The unique feature is the presentation of diagrams of instantaneous events during a single cycle so that the pages can be flipped, producing animation of a sort The instantaneous events are presented as a frontal and horizontal loop, and as scalar projections.

Perhaps the reviewer's Scotch background prejudiced him unduly, but the chief criticism centers about the large amount of wasted space and the limited information contained in the volume. The loop and scalar lead diagrams are confined to the upper outer quadrant of the right-hand page. The loops are tiny (the QRS loop in left ventricular hypertrophy is only 0.8 cm. and the T loop 0.2 cm in length). The legend is on an opposite page and generally confined to the upper half Quick calculation reveals that about 60 per cent of the illustrative section is blank page. Only eight illustrative conditions are covered Each requires about 40 pages to develop, many of which are repetitions (e.g., four pages of diagrams, four pages of legend to present an isoelectric S-T segment in a normal tracing).

The loops and electrocardiograms are presented in an idealized fashion, with no indication of the range of variation to be expected in each of the "syndromes." This is consistent with the author's aims, but the reviewer had expected more in view of the size and title of the volume.

There are a few quarrels with the content. Inferior myocardial infarction is presented with a normal T wave, whereas anterolateral myocardial infarction is presented with the expected abnormal T wave. Left ventricular hypertrophy is described as having accentuated leftward and posterior terminal forces. The initial forces in left bundle branch block are described as writing a Q wave in Lead V_1. The bibliography ...

Book reviews

THE 20TH CENTURY AND YOUR HEART. By H. J. Speedby, M.D., Westport, Conn., 1961, Associated Booksellers, 192 pages. Price $4 50.

This book was written by a physician for the lay public and represents an attempt to outline arteriosclerotic heart disease. Although it will probably be interesting to the layman, to the physician it will seem dull It is written simply enough but will still cause some confusion in the mind of an easily confused public

The book contains much in the way of factual and historical material, but it is doubtful that it will simplify the physician's task in caring for "the cardiac" As a substitute for consultation with the physician it will fall short.

INDEX-HANDBOOK OF CARDIOVASCULAR AGENTS, VOLUME 2, PARTS I AND II. Under the direction of Isaac D. Welt, Director, Cardiovascular Literature Project, Division of Medical Sciences, National Academy of Sciences of the National Research Council (Number 821). Washington, D. C., 1960, N A S.-N.R C., 1,568 pages. Price $15.

These two volumes entitled *Index-Handbook of Cardiovascular Agents* represent an excellent bibliography of reports on agents which influence the cardiovascular system. The purpose of these volumes is best described by Dr. Chauncey D. Leake, who wrote the Preface. He states:

"Communication between scientists is, at best, difficult. This is not to imply that there is a paucity of scientific periodicals and monographs. On the contrary, there are too many. Each specialized group, armed with its own language, desires its own forum.

"The present abundance of scientific publications makes excessive demands on the decreasing reading time of scientists; it critically overburdens abstracting and indexing—long the most productive tools for effective scientific communication.

"The flow of new chemical compounds alone, for example, is increasing at a rapid pace. Undoubtedly, many of these compounds are certain to have significant and important biological activity. To screen them effectively, to report them adequately, to judge their indications for medical or other uses satisfactorily, or to appraise them for general use in human welfare appropriately, is becoming a near impossible task.

"However, needs do not always wait upon the prudent and painstaking culling of volumes of printed material Scientists face the problem of retrieving pertinent information.

"It is with justifiable excitement, therefore, that we greet this present volume concerned with drugs acting upon the heart and circulation, undertaken by the Cardiovascular Literature Project of the National Academy of Sciences—National Research Council Under the skilled direction of Dr. Isaac D. Welt and his associates, this volume has emerged as more than a compendium of the literature. It stands as a new and unique approach, a model if you will, to scientific documentation.

"Though only a relatively few years of scientific publications are covered, the bibliography lists some 13,400 scientific communications, each analyzed and annotated with reference to the various drugs involved. Comprehensiveness has been coupled with penetrating analysis. For example, the title of a scientific paper frequently gives no indication of the drugs to which reference is being made, nor to the data concerning their biological effects. Analysis in depth by the Project staff has resulted in indexing and cross-indexing that obviates these troublesome omissions. Hence, prompt reference can be obtained in regard to the characteristics of the action of the drug concerned and with all deliberate speed.

"This volume, and those to follow, may be considered as a valuable working experiment. The success of this novel approach holds the promise of opening a new field in scientific documentation, with the result that indexes to scientific literature may become, in themselves, significant intellectual analytical tools."

These volumes should be available in medical libraries and large medical research centers, especially those concerned with cardiovascular research. Their existence should be made widely known, for it represents a fine service to scientists and a job well done.

MANAGEMENT OF HYPERTENSIVE DISEASES. By Joseph C. Edwards, A.B., M.D., F.A.C.P., F.A.C.C., Assistant Professor of Clinical Medicine, Cardiovascular Consultant to Division of Gerontology, and Consultant in the Hypertension and Cardiac Clinics, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo.; Cardiologist and Director, Hypertension Clinic, St. Luke's Hospital; Active Staff Physician, Deaconess Hospital, and Member of Consultant Staff, Missouri Baptist Hospital and St. Joseph Hospital, St. Louis, Mo.; Consultant, Council on Drugs, American Medical Association; Medical Consultant, Fifth Army of the United States, Office of the Surgeon General, Chicago, Ill. St. Louis, 1960, The C. V. Mosby Company, 439 pages. Price $15.

This monograph on the diagnosis and treatment of hypertensive disease and its complications was written by an author with a vast personal experience.

This is a detailed practical treatise on the problems of diagnosis and management, with many illustrative cases. Most of the practical points are covered, such as taking the blood pressure of the forearm and leg, breath-holding test, the forty-five-minute reduction in blood pressure by Regitine, omission of drugs before certain tests, and many others. An excellent section is given on secondary types of hypertension subject

American Heart Journal

October, 1962, Volume 64, Number 4

Editorial

Heart size

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Physicians of the pre-instrumental era took great trouble to learn and to teach to students a proper technique for the localization of the apex beat. The size or position of the heart, either as a first reading or for comparison over a period, was in their eyes a fact of great importance.

Radiology has abolished this measure, in some cases substituting in the physician's office a more scientific radiological technique for a somewhat inaccurate one, and in others—a retrograde measure—removing the x-ray facilities completely from the consulting room to the radiological department. For the fuller and more specialized cardioradiological measures this removal is clearly necessary, but for preliminary screening, and for the equally valuable function of measurement of heart size, the divorce has been harmful. Equally mistakenly could one advocate the delegation of the sphygmomanometer to some other department, for the heart can be measured as accurately as can the blood pressure, and nearly as quickly, by the physician himself, as part of the original clinical examination.

I, with Dr. B. G. Wells,[1] described a simple technique for this cardiometry, and proved it to be accurate, in a series of 159 blind consecutive measurements of transverse cardiac diameter, with a margin of error not exceeding 0.5 cm. in 77 per cent, and 0.6 cm. in 92 per cent. A long clinical experience has confirmed the value and reliability of the procedure.

The heart may be found to be so small that organic disease can thereby be excluded. An example was that of a man admitted for his fourth attack of very severe mid-chest pain. Inversion of the T wave in Lead aV_L had suggested a coronary ischemia, but skepticism aroused by the small heart prompted further search, which revealed an esophageal diverticulum.

Nonvariation of size over a period may confirm cardiac health. A 47-year-old man suffered, in 1952, an anterolateral myocardial infarct, with typical S-T elevation and subsequent changes of resolution, shown in Lead V_2 to Lead V_6. His heart-size measurement was originally 12.2 cm., and subsequent figures were 11.8, 12.4, 12.6, 12.0, 11.8, 12.1, 12.0, 12.0, 11.6, 12.4, 12.0, and 12.3, at intervals over the next 10 years.

The harmlessness of his hypertension (208/112 mm. Hg) was shown in another man whose heart size was 12.0 cm. in 1947, whereas in 1960, when he was 70 years of age, the increase was only 1.5 cm. to 13.5 cm. (blood pressure of 230/132 mm. Hg).

Diminution in size can be measured with equal profit. The heart of a woman who was treated surgically for mitral stenosis di-

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be a recommended reading list instead of a true bibliography. Most major ECG texts are included, but the relevance of some (e.g., those confined to arrhythmias) to this volume is obscure.

In summary, this is a book with a limited aim. This aim seems to have been accomplished, but the reviewer would have preferred a higher ratio of information to page surface.

Announcements

A Graduate Course in Medical Hypnosis is being offered to physicians and dentists by the University of Pennsylvania Graduate School of Medicine. The Department of Neurology and Psychiatry is in charge of organizing the sessions.

The 96-hour course will consist of 24 weekly afternoon sessions, beginning Oct. 3, 1962.

At the present time, it is the only course offered which meets recommendations made by the American Medical Association's Committee on Hypnosis.

During the first part of the course, basic concepts of hypnosis will be taught through lectures on psychiatry and hypnosis, demonstrations, and supervised practical work in hypnosis.

The latter part of the course will cover clinical applications of hypnosis. Here there will be sessions limited to psychiatrists, and other sessions limited to general practitioners, dentists, and specialists other than psychiatrists.

The course will be given at the Institute of the Pennsylvania Hospital, 111 North 49th St., Philadelphia 39, Pa.

The teaching staff of eight is headed by Lauren H. Smith, M.D., Professor and Chairman of Psychiatry, Department of Neurology and Psychiatry at the Graduate School of Medicine, and Administrator of the Hall-Mercer Hospital, Pennsylvania Division. Dr. Smith is also Chairman of the American Medical Association Council on Mental Health. The staff will include Dr. Harold Rosen, Head of the American Medical Association's Committee on Hypnosis.

The University of Texas Postgraduate School of Medicine will sponsor a Clinical Symposium on The Practical Treatment of Hypertension, Sept. 20-22, 1962. The Symposium will be held in the auditorium of The University of Texas M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, Tex.

Guest speakers and their topics will be as follows: Dr. James Conway, University of Michigan Medical Center, Ann Arbor, Mich.: "Current Concepts and Theories Regarding the Etiology of Essential Hypertension and Its Natural History." Dr. Arthur Grollman, The University of Texas Southwestern Medical School, Dallas, Tex.: "Metabolic Observations in Essential Hypertension and the Role of Associated Vascular Disease and Its Influence on Therapeutic Considerations." Dr. W. R. Wilson, Johns Hopkins University School of Medicine, Baltimore, Md.: "The Effects of Newer Hypotensive Drugs on the Hemodynamics of Hypertension." Dr. Walter Kirkendall, University of Iowa School of Medicine, Iowa City, Iowa: "Indications for Treatment, Present-Day Drug Therapy of Essential Hypertension, and Changes Observed in the Fundi of Hypertensive Patients During Treatment and in the Absence of Treatment." Dr. Leon Goldberg, Emory University, Atlanta, Ga.: "Alpha-Methyl Dopa and Guanethidine as Therapeutic Agents in the Treatment of Essential Hypertension and Pheochromocytoma, Its Diagnosis and Treatment." Dr. Ray F. Gifford, Cleveland Clinic, Cleveland, Ohio: "The Diagnosis and Treatment of Renovascular Hypertension and the Treatment of Hypertensive Emergencies." Dr. Reginald Smithwick, Boston University, Massachusetts Memorial Hospitals Medical Center, Boston, Mass.: "Sympathectomy, Adrenalectomy, and Nephrectomy in the Treatment of Hypertension."

For further information write: Office of the Dean, The University of Texas Postgraduate School of Medicine, 102 Jesse Jones Library Building, Texas Medical Center, Houston 25, Tex.

The Information Explosion—Its Challenge and Problems will be the theme of the 19th Annual Meeting of the American Medical Writers Association at the Sheraton Park Hotel in Washington, D. C., Oct. 12 and 13, 1962. The first day will be devoted to what medical journal editors, authors, educators, pharmaceutical companies, and medical writers can do to meet the challenge of the flood of new medical information. On the second day, the meeting will consider the promise of recent advances in information storage and retrieval, in utilization of the "newer" communication media (films, radio, television, recordings, and programmed instruction), and in professionalism among medical communication personnel.

For details and registration forms, contact John Sargeant, Chairman of the Local Arrangements Committee, Medical and Chirurgical Faculty of Maryland, 1211 Cathedral Street, Baltimore 1, Md.

Clinical communications

Arrhythmias induced during intracardiac catheterization

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Arrhythmias are induced frequently during cardiac catheterization. In most instances they are benign and short lived. Little information is available in most of the standard texts concerning this subject.[1-3] The mortality associated with catheterization is approximately 0.1 per cent; when deaths do occur, they are usually caused by arrhythmias. Because we found no recent studies on arrhythmias which occurred during catheterization, we reviewed 942 cardiac catheterizations done in the University of Alberta Hospital, in order to determine the relative frequency and duration of the various types of arrhythmia.

Methods

The ages of the patients in this series ranged from 2 weeks to 51 years. Six hundred and twenty-four patients had congenital heart disease, 115 had rheumatic valvular heart disease, and there were single patients with primary pulmonary hypertension, myxoma of the left atrium, and normal findings. Seven hundred and forty-two patients were catheterized, but, in addition, 200 of these patients had a second catheterization at a subsequent examination. Therefore, we have considered that the population at risk for the purpose of this study was 942.

Infants and children who weighed less than 45 pounds were sedated with a mixture of meperidine, chlorpromazine, and promethazine, as recommended by Keith, Rowe and Vlad.[4] Older children and adult patients were given secobarbital and meperidine. General anesthesia was not used.

Catheters were sterilized with heat (250°F. for 10 minutes), and, although they maintained their form, they were not stiff. The size of the catheters used was either 5F or 6F, depending upon the size of the patient.

The electrocardiogram and a simultaneous pressure tracing were monitored on an oscilloscope during the catheterization. In addition to the usual photographic recording made of the various pressures the tracing was recorded when arrhythmias appeared. Short bursts of ventricular premature beats which occurred with considerable regularity when the tip of the catheter was in the right ventricle, as well as isolated atrial and nodal premature beats, when the tip of the catheter was in the right atrium, were not classed as arrhythmias for the purpose of this study.

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minished in size from 14.2 cm. to 12.8 cm. after operation, and that of a man with myxedema from 13.7 cm. to 12.0 cm. after a course of thyroxine.

Innumerable examples in all varieties of heart disease have convinced me, after a clinical experience of over 30 years in consulting practice, of the diagnostic and prognostic value of routine heart-size measurement as part of the clinical examination. These few paragraphs may perhaps assist in the removal of a cardiological clinical "blind-spot."

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reverted to normal only after several hours. One patient with atrial flutter and one with a nodal rhythm also had prolonged arrhythmias. Three patients had persistent arrhythmias which lasted more than 3 days—one patient had atrial flutter, one had atrial fibrillation, and one had a right bundle branch block.

Most arrhythmias reverted to normal spontaneously (69 per cent). Sometimes, normal rhythm was restored by further manipulation of the catheter in the right atrium. Less frequently, the arrhythmia ceased after premature ventricular beats occurred during withdrawal of the catheter through the right ventricle.

Specific treatment was used in 18 patients (31 per cent). This consisted of lanatoside C in 10, procaine amide in 5, quinidine and procaine amide in 2, and lanatoside C with procaine amide in 1. In only one instance was treatment urgently required because of the rapid appearance of shock associated with a supraventricular tachycardia. This patient, a 10-year-old girl, was catheterized 2 days postoperatively because disruption of a repaired ventricular septal defect was suspected. The arrhythmia was converted to normal rhythm within 10 minutes after partial digitalization.

The various methods for inducing vagotonia were used with indifferent success for the treatment of arrhythmias which persisted longer than a few minutes. Better results were usually obtained with the use of intravenous fast-acting digitalis.

Discussion

The incidence of significant arrhythmias which occurred during the course of catheterization has been reported in only a few large series of patients. Kjellberg[1] reported 22 arrhythmias in 837 catheterizations (2.6 per cent); Wood[3] noted 111 arrhythmias in 1,000 catheterizations (11.1 per cent), and Keith,[4] 107 in 700 (15.3 per cent). The earlier studies on arrhythmias during catheterization were carried out on small groups of patients and provide little valid basis for analysis.[6-9] It is difficult to compare results from different centers because the criteria for reporting arrhythmias during catheterization are variable. We have not included minor and momentary arrhythmias, as stated earlier. The occurrence of 58 arrhythmias in this report of 942 catheterizations (6 per cent) was somewhat less frequent than that found by either Keith or Wood, but exceeded the incidence reported by Kjellberg. However, Kjellberg's observations were not presented in detail and may have excluded arrhythmias which were included in the other series. Arrhythmias probably occur in 5 to 15 per cent of the patients who undergo cardiac catheterization.

Michel and associates[10] found the highest incidence of arrhythmias during catheterization in those patients with congenital heart disease. However, his series consisted of only 23 patients with congenital, and 5 patients with rheumatic valvular, heart disease. The other 105 patients had hypertensive heart disease, coronary artery heart disease, toxemia of pregnancy, and cor pulmonale. From a review of his data there appeared to be no difference in the number of arrhythmias produced in patients with congenital heart disease when compared with patients with rheumatic heart disease. In our series, which included 121 catheterizations of 115 patients with rheumatic valvular heart disease, and catheterization of more than 700 with congenital heart disease, no difference in the incidence of arrhythmias in these two groups was found.

Further study of the 200 patients who had a second catheterization indicated that the appearance of an arrhythmia during the first procedure did not enhance the possibility of the same or another arrhythmia at a second catheterization.

We have no information from this study which would enable us to relate the incidence of arrhythmias to the size of the catheter. However, Keith[4] found that paroxysmal atrial tachycardia occurred twice as often with the use of a 6F catheter as with a 5F, and that no complete atrioventricular blocks were produced during catheterization with a 5F catheter. It is obvious that the resilience as well as the size of the catheter must be taken into consideration. The method chosen for sterilizing cardiac catheters appreciably affects their stiffness. For this reason it is difficult to assess the importance of the

Table I. Types of arrhythmias induced during catheterization of the right heart in 942 patients

Arrhythmia or conduction defect	*Number of patients*	*Diagnosis*			*Catheterization site*		*Duration*		
		Congenital	*Rheumatic*	*Others*	*R.A.*	*R.V.*	*Minutes*	*Hours*	*Days*
Sinus bradycardia	1	1			1		1		
Supraventricular tachycardia	30†	28	1	1	26	4	24	6	
Atrial flutter	4*	2	2		4		2	1	1
Atrial fibrillation	3	1	2		2	1	2		1
Nodal rhythm	3	3			2	1	2	1	
A-V block, incomplete	2	2				2	2		
Bundle branch block	6†	4	1	1		6	5		1
Bigeminal rhythm	4	4			2	2	4		
Ventricular tachycardia	5*	2	2	1	1	4	5		

* †Single patient with two arrhythmias

The position of the tip of the catheter was determined by fluoroscopic examination and was confirmed by the intracardiac pressure tracing.

Results

Arrhythmias occurred during the course of cardiac catheterization in 56 patients (6 per cent). In one instance, both a nodal tachycardia and a bundle branch block occurred at different times during the course of a single catheterization. In a second patient, ventricular tachycardia was succeeded by atrial flutter. In both cases, each of the arrhythmias is listed in Table I, accounting for a total of 58 arrhythmias in 56 patients.

The most common types of arrhythmias were supraventricular in origin. Because it was difficult to be certain of the exact type of supraventricular tachycardia when it was of short duration, we have included recognized nodal and atrial tachycardias in a general group of supraventricular tachycardia which accounted for 52 per cent of the total. None of the eight other classes of arrhythmias or conduction defects occurred with any frequency. Bundle branch block which was induced during intracardiac catheterization involved the right bundle in 5 of 6 patients. A single intermittent left bundle branch block was observed in a patient with a myxoma of the left atrium.

Fewer patients with rheumatic than with congenital heart disease were catheterized. Despite the smaller number of patients with rheumatic heart disease the frequency of arrhythmias in this group during catheterization (6.6 per cent) was almost the same as that found in patients with congenital heart disease (5.7 per cent).

It was obviously difficult to be sure of the precise position of the tip of the catheter at the moment an arrhythmia appeared. With this reservation, however, these data have been included in Table I. Most of the arrhythmias (65.5 per cent) occurred while the catheter was being manipulated in the right atrium. In many instances, it is probable that the tip was close to the tricuspid valve.

In all patients who developed bundle branch block or A-V block the tip of the catheter was in the cavity of the right ventricle. One patient developed a short bout of ventricular tachycardia while the catheter appeared to be in the right atrium.

The single patient with sinus bradycardia developed this arrhythmia when the catheter was passed from the right to left atrium through a patent foramen ovale.

The arrhythmias induced by catheterization lasted only a few minutes in 47 of 58 episodes. In 3 patients who developed supraventricular tachycardia, and in 3 who had nodal tachycardia the rhythm

zation of the right side of the heart was reviewed in 942 catheterizations of 742 patients. Significant arrhythmias, apart from occasional atrial, nodal, and ventricular premature beats, appeared in 58 patients (6 per cent).

The arrhythmias lasted for a matter of minutes in 81 per cent, for several hours in 14 per cent, and for longer than 1 day in 5 per cent.

Seventeen per cent of the patients who developed arrhythmias were treated with intravenous lanatoside C. The other patients developed a normal rhythm spontaneously. No fatal arrhythmias occurred.

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size of the catheter in relation to arrhythmias when data are obtained from different centers in which various methods of sterilization and preparation are used.

In our experience, most arrhythmias occurred when the catheter lay in the right atrium. The exceptions were in patients who developed atrioventricular block, bundle branch block, bigeminal rhythm, and ventricular tachycardia. As might be expected, these usually occurred when the catheter was in the right ventricle. Reference has already been made to the single patient who developed sinus bradycardia on each occasion when the catheter was passed through a foramen ovale. In an earlier study,[11] we found that arrhythmias occurred five times more frequently in patients who were catheterized through a left persistent superior vena cava (with 38 per cent developing arrhythmias), when compared with the whole group. Those patients with a left superior vena cava who developed arrhythmias are included in this study but have not been categorized separately.

Keith[4] found that bundle branch block occurred five times more often in patients less than 1 year old, when compared with the other patients in his series. Only one of our 6 patients who developed a bundle branch block was less than 1 year old (2 weeks), the others were 1½, 10, 35, 40, and 51 years old. Fowler[8] described the appearance of right bundle branch block in 7 patients during the course of venous catheterization of the heart in 110 patients. The incidence of 6.4 per cent in his series is ten times that found in our patients, but the explanation for this difference is not apparent. One would suspect that arrhythmias and conduction defects might be induced more frequently in patients with cardiac abnormalities. In fact, none of Fowler's patients had primary cardiac disease. Simonson[12] attributed the transient appearance of right bundle branch block, which appeared during catheterization of a 50-year-old man, to impingement of the catheter on the septum, and cited experimental evidence in support of this explanation. In addition, right bundle branch block (both complete and incomplete) has been produced recently in normal subjects by applying pressure on the right ventricular septal surface with an electrode catheter.[13] The electrocardiographic changes lasted only a few minutes in each instance. We suspect that more persistent forms of block might well occur if more pressure were to be exerted on the septum during catheterization. In all 5 of our patients who developed a right bundle branch block the conduction defect appeared when the catheter was in the right ventricle. We believe that differences in the incidence of right bundle branch block may be accounted for by variations in individual techniques of catheterizing the right ventricle and by the properties of the catheter used.

The treatment of arrhythmias induced during catheterization usually presented no problem. Many arrhythmias reverted spontaneously upon withdrawal of the catheter, manipulation of the catheter in the right atrium, or after one or two ventricular premature beats. Eighteen of the patients required specific treatment for their arrhythmias, as outlined in the section on results. Reference has already been made to the only patient for whom treatment was urgently required. However, the production of rapid arrhythmias in patients with severe valvular obstruction or in infants under 18 months of age may lead to acute heart failure. Although his cardiac catheterization was uneventful, a 4-year-old boy with severe pulmonary valvular stenosis spontaneously developed supraventricular tachycardia (250 per minute) and presented with acute cardiovascular collapse on one occasion prior to investigation. He recovered uneventfully after his rhythm was restored to normal. In addition, a second child was treated several times up to the age of 2 years for acute failure which was precipitated on each occasion by supraventricular tachycardia in the absence of any congenital cardiac disease.[14] The induction of arrhythmias during a catheterization could be expected to precipitate failure in both of these types of patient during cardiac catheterization and would require immediate treatment.

Summary

The occurrence of arrhythmias which appeared during the course of catheteri-

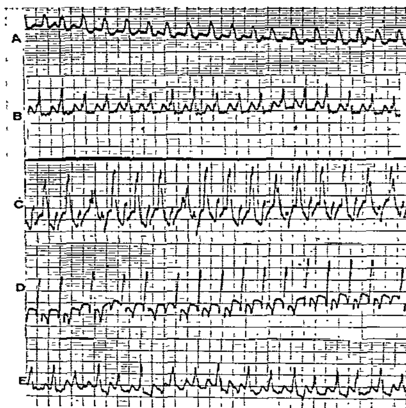


Fig. 1. A, Lead II on admission. Sinus tachycardia at a rate of 155 per minute is present. B, Lead II during episode of chest pain. Note change in "P"- wave configuration. Rate is essentially unchanged C, Esophageal lead discloses presence of second atrial wave superimposed on an already widened QRS complex. This can be easily demonstrated in ventricular complexes 3, 7, 11, 15, and 16. D, Esophageal lead after further digitalis therapy reveals atrial flutter with varying degrees of atrioventricular block E, Lead II after large amounts of digitalis is typical of atrial flutter.

a well-controlled ventricular response developed (Fig. 4). Because of an increasing response in his ventricular rate and increasing signs of congestive heart failure, digoxin, 0.25 mg., was started on the fifth hospital day. When the ventricular rate was well controlled, quinidine sulfate, 0 2 Gm every 2 hours, was cautiously started, with frequent electrocardiographic monitoring. Three hours after the fifth and last dose of quinidine there was a marked change in the electrocardiogram (Fig. 5) The QRS complexes appeared to be unchanged. There was no electrocardiographic evidence of atrial activity, and the ventricular rate was observed to be much more regular. Even after the right precordium was explored, no evidence of atrial activity could be detected.

An esophageal lead was passed, and, at the 25-cm. level, typical atrial flutter waves were observed with atrioventricular dissociation and a nodal pacemaker

Since we could not be certain whether this arrhythmia reflected digitalis, quinidine, or combined toxicity, all medications were stopped. On the following morning, the electrocardiogram revealed normal sinus rhythm with first-degree atrioventricular heart block (Fig 6).

Discussion

Most problems in clinical electrocardiography can be resolved by the standard 12-lead electrocardiogram. In many hospitals, in addition to the 6 standard and 6 precordial leads, a right anterior chest lead (V_{3R} or V_{4R}) is also used to "probe" more extensively the right ventricular potential.

On occasions, however, insufficient information is obtained with these 12 (or more) leads. The precise diagnosis of an ectopic rhythm presents one of the clinical opportunities in which the addition of the esophageal lead may be especially rewarding.[1-3]

Esophageal electrocardiography

Selected clinical applications

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Frequently in clinical electrocardiography a concomitant disturbance in rhythm and intraventricular conduction is encountered. The following illustrative case reports demonstrate the value of esophageal electrocardiography in resolving the problem of differentiation between these disturbances in the heartbeat.

Case reports

Case 1 (*Fig 1*). This 74-year-old white man with both chronic obstructive pulmonary emphysema and coronary artery heart disease was hospitalized because of chest pain, cough, and fever. Previous electrocardiograms revealed complete left bundle branch block with normal sinus rhythm. Despite vigorous supportive treatment there was progressive clinical deterioration. The routine electrocardiogram was essentially unchanged when compared with previous records, except for a slight change in the configuration of the P wave. Carotid sinus pressure did not alter the rhythm. Because of the possibility of a second atrial wave superimposed on an already widened QRS complex, an esophageal electrocardiogram was taken This revealed atrial flutter with 2:1 atrioventricular block. Additional digitalis was given and a higher degree of atrioventricular block obtained. Only after 3:1 atrioventricular heart block had been produced did the standard electrocardiogram clearly demonstrate atrial flutter.

Case 2 (*Fig. 2*). A 67-year-old white man with a past history of myocardial and pulmonary infarction was hospitalized because of dyspnea and hemoptysis. Examination at the time of his admission to the hospital revealed heart failure and obstructive pulmonary emphysema. After initial improvement with anticoagulants, digitalis, and diuretics, the patient suddenly experienced anterior chest pain which was associated with tachycardia. The standard electrocardiogram revealed a ventricular rate of 150 per minute with what appeared to be a second atrial wave present within the terminal portion of the QRS complex. There was no change in the heart rate or QRS configuration with carotid sinus pressure. A tentative diagnosis of either atrial tachycardia or flutter with 2:1 atrioventricular block was made. An esophageal electrocardiogram, however, demonstrated the presence of sinus tachycardia with no evidence of an atrial ectopic rhythm. Serial electrocardiograms were consistent with the clinical impression of an acute myocardial infarction.

Case 3. A 66-year-old white man was hospitalized in congestive heart failure secondary to arteriosclerotic coronary artery heart disease. The initial electrocardiogram disclosed complete left bundle branch block and bigeminy (Fig. 3).

Since the patient had been on large doses of chlorothiazide in addition to Gitaligin, 0.75 mg. daily, digitalis intoxication was presumed to be complicating and contributing to the congestive heart failure. Laboratory studies at the time of his admission to the hospital revealed mild hypokalemic alkalosis.

Potassium chloride was administered orally in addition to supportive measures which were directed toward the congestive heart failure. Within 36 hours the bigeminy had disappeared and the patient was markedly improved.

On the third hospital day, atrial fibrillation with

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Fig. 3. Lead I at the time of admission. Left bundle branch block, first-degree atrioventricular heart block, and bigeminy are noted.

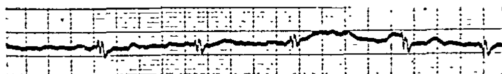


Fig. 4. Lead II on third hospital day. Atrial fibrillation with a well-controlled ventricular rate is observed.

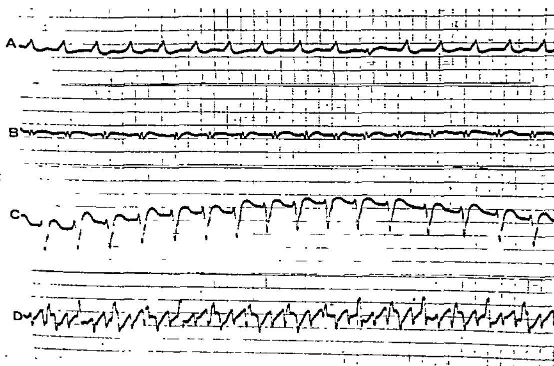


Fig. 5. *A*, *B*, and *C*, Leads I, II, and V_{3R}, respectively, demonstrating apparent loss of atrial activity. *D*, Esophageal lead (25 cm), demonstrating atrial flutter with probable atrioventricular dissociation.

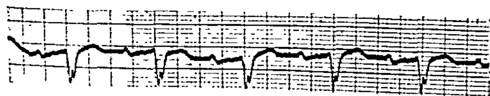


Fig. 6. Lead V_1. Normal sinus rhythm, first-degree atrioventricular block, and left bundle branch block are present.

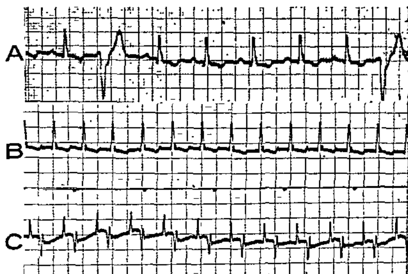


Fig 2. *A*, Lead II on admission. Normal sinus rhythm at a rate of 90 per minute is present. Occasional premature ventricular contraction is also present. *B*, Lead II after onset of severe chest pain. Note notching of terminal portion of QRS which suggests the presence of second P or F wave. *C*, Esophageal lead recorded immediately after *B* demonstrates sinus tachycardia There is no evidence of an ectopic atrial activity.

At the Heart Station of the Veterans Administration Hospital, Coral Gables, Florida, the esophageal electrocardiogram is frequently utilized in the study of disorders of the heartbeat. The Nyboer esophageal electrode with ten outlets (0 to 45 cm.) is used, attached to the unipolar precordial lead. The esophageal electrode is lightly lubricated and passed into the stomach in the manner of a Levine tube. With the ten outlets, the level of the recording lead can be rapidly changed without moving the external rubber tubing.

In a survey of 100 hospitals which were picked at random throughout the United States, it was found that 33 utilize esophageal electrocardiography. Only 4 hospitals made frequent use of the esophageal lead, however, in the diagnosis and management of cardiac arrhythmias.

When disturbances in rhythm coexist with delayed intraventricular conduction, the clinical problem may be very complex. When atrial and ventricular activity occur simultaneously, there may be fusion of the P wave or flutter wave with the QRS complex. If bundle branch block has been observed previously, a notched QRS complex, which in reality is P plus QRS, may be interpreted merely as further delay in intraventricular conduction.

Similarly, in a patient with known bundle branch block, a supraventricular tachycardia may develop, in which the second atrial wave (P or F) may go undetected in the standard leads. This becomes of major importance in patients in whom atrial flutter or paroxysmal auricular tachycardia with 2:1 block develops. In a previous study,[4] the value of the esophageal electrocardiogram was demonstrated in the differential diagnosis of rapid atrial arrhythmias associated with aberrant ventricular conduction. With the widening of the QRS complex which results from "bundle branch fatigue" (aberrant conduction), discernible atrial activity may not be evident when one is using the standard 12-lead electrocardiogram. In the 3 illustrative cases, addition of the esophageal lead prevented errors in diagnosis and management.

In the first patient, atrial flutter was demonstrated with the aid of esophageal electrocardiography. What had been interpreted as a notched and widened ventricular complex was, in reality, a flutter wave superimposed on the QRS complex.

In the second patient, the presence of an atrial ectopic rhythm was suspected because of a peculiar notching in the terminal portion of the QRS complex. Eso-

The impact of congenital heart disease upon the family

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Sally Gane, M.A.
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It is accepted that any disease must have an effect upon the mind and the body. Illness must also affect the family of the sick person, and this interplay of events with the family is a basic consideration of good pediatric practice. Various illnesses will affect individuals and their families in different ways, but diseases of the heart, with their chronicity and age-long association of death, seem likely to have a greater impact. Anxiety is inseparable from illness, and the "calling of the doctor" is commonly a symptom of the need to share responsibility. However, there is little reliable information concerning the extent of fear and other reactions in the families of the disabled, this is true for chronic illness in general, and for congenital heart disease in particular.

Therefore, with this vague background of ignorance, we decided to investigate a series of families who had one thing in common—a child with inborn heart disease. Clearly enough, this implied "selection" from the start. The reader should bear this "selection" in mind throughout.

Common knowledge tells us that many people try, deliberately or unconsciously, to please the doctor. Therefore, in this study, the physician retained his position of medical attendant and interpreter. The other issues were explored by a skilled social worker, who administered a questionnaire. This served as a guide to finding out what was going on; in our ignorance of what really does go on in such a family, we tried to answer several leading questions. Incidentally, we acquired a good deal of knowledge about the income, insurance coverage, number of houses without toilets, etc. For those who are interested in these aspects, Tables I-IX are included.

The main points at issue were: What are the effects upon family life of congenital heart disease—*as the family sees it*? What does an "average" family know about congenital heart disease? A lot? A little? Do people really understand what doctors talk about? Do doctors help families in adjusting—whatever "adjusting" means? Is this child hard to handle? And so on.

One hundred and fifty families were questioned. About half were studied after at least one visit to the cardiac clinic at University Hospitals; we called this the "retrospective group." The others were questioned at the first visit, often before any diagnosis was given. This we called the "prospective group." The survey was repeated in the families of 25 children on whom surgery was performed. All patients were thought, on good clinical grounds, actually to have congenital heart disease. All underwent special investigations (angi-

This study was carried out at the University Hospitals, University of Wisconsin, Madison, Wis.
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phageal electrocardiography clearly defined regular atrial activity with prolongation and slurring of the terminal phase of ventricular depolarization.

In the third patient also, the necessity of clearly defining atrial activity electrocardiographically is demonstrated. Although the standard electrocardiogram failed to disclose atrial activity, atrial flutter was observed with the esophageal lead.

Summary

It would appear that more widespread use of the esophageal lead in patients with delayed intraventricular conduction may be fruitful in the recognition of unsuspected atrial arrhythmias. Use of the esophageal electrocardiogram may also be of value in the management of atrial arrhythmias associated with bundle branch block.

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Table VI. Occupation of father (%)

Self employed	Business	4.6
	Professional	0.6
	Farmer	14.0
	Other	2.6
Employed	Laborer	30.5
	Semi-skilled	25
	Skilled	20.6
	Professional	0 6
	Miscellaneous	1 2

Table VII. Occupation of mother (%)

Home duties	83 2
Employed part time	12 2
Employed full time	4 0
Student	0 6

Table VIII. Family income (%)

$1,000 or less	12
$3,000 to $3,000	52
$7,500 to $5,000	21
$10,000 to $7,500	3 2
$10,000+	2 4
Reticent about income	6 4

Eighty-five per cent had some form of medical insurance and 50 per cent were home owners.

Table IX. Housing (100 families) (%)

City	39
Town	34
Rural	27
"Adequate"	73
All facilities	84

based principally upon the invalid belief that the child would "outgrow" the condition. At a later stage in the questionnaire, when the corollary question, "Do you believe he can be cured by surgery?" was asked, the replies were quite variable—"Don't know" was the usual answer. If a positive "yes" was given, this was usually related to knowledge of a successful operation in another case.

The families were asked what they thought caused the defect. Fifty-six per cent didn't know; the remainder had varied, sometimes bizarre ideas, mostly evading specificity by calling it a "pregnancy problem" (44 per cent) or "heredity" (11 per cent). About 6 per cent had an element of "divine retribution" in their ideas. We got the (strictly uncontrolled) impression that feelings of guilt blocked some answers to this one. A history of all types of heart disease in the family or near relatives was claimed in about 60 per cent. This figure seems to be a reasonable one. However, only a fraction inferred that such a history caused the defect in their own child.

In most cases (69 per cent) the diagnosis was made by the patient's private physician—before the age of 5 years in 94 per cent of the patients. The diagnosis was usually revealed (55 per cent) to the mother alone. As to their immediate reactions, the usual ones were "fear" ("worry," "fright," "concern") in 90 per cent of the group. "Surprise" was often (16.5 per cent) expressed at the same time; other feelings were frank disbelief (6.6 per cent), "guilt," and "betrayal by God" (one case). Only 4 per cent registered optimism, and 1 per cent "acceptance."

Considering the reactions of fear expressed, it is probably gratifying that 67 per cent found the first explanation understandable. The others had no clue; of the 150 families, 13 per cent said that, in their opinion, no explanation had been given to them. There seemed to be no reason to doubt their word on this point. The majority (75 per cent) of the total expressed themselves to be "satisfied" with their initial consultation. In the 25 per cent who were "dissatisfied," there was no real correlation with the comprehensibility of the explanation. These statements, however, should not be taken completely at their face value, because 40 per cent sought other medical advice *on their own initiative*. Again, these people were almost equally represented in the initially "satisfied" and "dissatisfied" groups. The "other opinions" were mostly sought from other general practitioners, pediatricians, and university clinics (in descending order of incidence). "Nonmedical" opinions were sought only once.

The troubles of rearing the affected child were superficially explored. Some 50

Table I. *Length of marriage* (%)

< 1 yr.	1 3
1–3 yr.	6 6
3–10 yr.	40 0
10–15 yr.	25 3
15–25 yr	22 0
25 yr. +	2 6
Father deceased	0.6

Table II. *Size of family* (%)

Singletons	10
2–3	49
4–5	28 5
6+	12 5

(45% "Planned")

Table III. *Family health*

	Mother (%)	*Father* (%)	*Siblings* (%)
Good	8	10 6	7 1
Average	7 7	71 0	11 5
Poor	15 0	17 3	17 5
Deceased	—	0 6	—

ography, cardiac catheterization) which confirmed this impression.

In the expectation that we might be able to find the reasons why some families compensated and others did not, the "family and its background" was worked over. Encompassing this were such facets as income, age of parents, education of parents, standard of housing, etc. This fact-finding mission showed us that people who come to a university hospital clinic tend not to have much money; this has been confirmed for other hospitals and other diseases. However, none claimed really to be on the bread line; their own assessment of income level was "adequate" in 48 per cent, "barely adequate" in 36.5 per cent, and "totally inadequate" in 15.5 per cent. This appears to be a normal distribution of belief irrespective of income group. Most families had more than one child, and comparisons with census figures suggested no real difference in the number of children in the family, nor undue loading with one sex or the other. In other words, this "selected" community seemed to be reasonably representative of those who might attend a university clinic, and perhaps our conclusions might have some value when applied to similar groups.

Well, what did those people know about congenital heart disease before their own problem erupted? The answer is simple—only about 12 per cent had more than the most superficial knowledge of the condition. After personal involvement the percentage rose to 58, but about half of these (30 per cent) had only the most rudimentary facts. Curiously enough, 60 per cent of those questioned knew (or thought that they knew) of other cases of congenital heart disease in their district. The group as a whole thought that congenital heart disease was "common." The actual incidence is, of course, about 1 per cent of all live births. In other words, bad news travels fast and has a wide coverage. We tried to find out what the family's idea of prognosis was. Sixty per cent thought that the child's life would be considerably shortened; 25 per cent (suspiciously high ?) had "no opinion," and the rest thought that there would be no effect upon the length of life of the child. When asked whether the condition was curable without surgical help, some 40 per cent replied "yes." This optimism was

Table IV. *Age of parents*

Age (yr.)	*Mother* (%)	*Father* (%)
Under 20	2	0.7
20–30	38	24
31–41	47.3	48
41–45	10 3	18
50+	0 4	3.3

Table V. *Education*

Length	*Mother* (%)	*Father* (%)
<8 yr.	3 3	6 6
8 yr.	19.3	21 2
9–12 yr.	56.5	53
College	20.6	14.6
Advanced degree	—	4

than confidence. About two thirds of the group (all except one mother who was in the fertile age) planned to have more children—which is perhaps a fairly basic measure of their confidence; of the whole group, 20 per cent believed that there was a high chance that any following child would be abnormal; 70 per cent thought that such a possibility was remote, and the remainder could not give an opinion.

Since surgery is the answer to most congenital cardiac defects, the attitudes of the family to this were explored. When the topic was brought up, 70 per cent thought that they would react positively. The remainder, who answered in the negative, did so because they were ignorant of this aspect of the care of the disease. The majority (83 per cent) agreed that "surgery and short-term risk" were more tolerable than "prolonged anxiety." The positive acceptance of surgery rose to 86 per cent if a definite decline in life expectancy was forecast. Again, at this stage of the questioning their past reactions to the diagnosis were recapitulated, 76 per cent again described reactions of fear (or variants). Over all, at the stage of surgical discussion, 60 per cent expressed optimism, whereas the rest expressed guarded or frank pessimism. In an effort to learn whether parents would be influenced by the way in which a suggestion for surgery was made, we inserted the following questions: (a) "Are you in favor of surgery if the chances of failure are 25 per cent?" (b) "Are you in favor of surgery if it would be 75 per cent successful?" The two were widely separated in the questionnaire. The positive and negative answers to each question were not statistically different.

The study has shown that fear and its variants are widespread in the family, and that the brothers or sisters of the patient may react more frequently than has been suspected. Since anxiety is widespread and prolonged, and adjustment not invariable, the pediatrician has a responsibility to anticipate the common problems It may be said that comprehensible explanation drives out fear, and that this was the usual basis for the leading role of the physician in helping the family to adjust.

The reasons for anxiety are many, and often change within the same family. However, the study suggests points of community which must be dealt with in all families. The following is the skeleton of an approach which may anticipate most difficulties.

The first essential is to have an adequate idea of the diagnosis. This is usually clinically obvious, and is the basis for the prognosis, which, in turn, depends upon the possibility of surgery. In the case of children in whom the diagnosis is in some doubt, the parents should be told that the explanations given are provisional. In all cases, the situation should be crystallized as soon as possible. When this has been done, the responsible pediatrician should sit down with the parents and review the situation with them. A simple diagram of the circulatory system is essential for this, since most parents are mechanically minded enough to appreciate explanations given on a physiologic basis The study suggests that emotional or other reasons may prevent the full impact of the explanation. Therefore, repeat it, and beware of the small percentage who cannot accept the possibility that their child has heart disease. This fraction will respond sometimes to seeing the "abnormal" x-ray films for themselves, or another opinion should be sought immediately. There is no point in encouraging false hopes in any family, therefore, the routine statement would be, "The child will not grow out of this problem; it is here until surgery fixes him up." Once accepted, this builds the foundation for the remainder of the relationship.

The fear that the child may die suddenly should be exorcized forthwith. Sudden death is an unusual mode of exitus, except perhaps in the case of tricuspid atresia. Therefore, the parents should be reassured about this possibility.

We cannot give any figures about feelings of guilt from this study. However, since a "pregnancy problem" is a major cause of concern to many parents, it is humane to make to all parents a simple statement such as "The exact cause of your child's defect is not known, but it is not due to bad heredity in either family, nor is it due to anything you did or didn't do during

per cent thought that the child with congenital heart disease gave rise to some problems: mostly (in 50 per cent), these were difficulties in disciplining the child, but feeding difficulties (in 20 per cent) reflect a common symptom of the disease also. The rest thought that more general care and attention were necessary. Nearly half (43 per cent) of the families said that "spoiling" of the afflicted child occurred; continuing anxiety was perhaps reflected in the fact that 14 per cent of these children shared the parental bed—even if adequate accommodation was available. "Checking at night"—a common practice with normal first-born infants for a month or two—occurred in 64 per cent of the families, althouth the majority of patients were not infants. Indeed, 10 per cent of mothers or fathers "checked up on the child constantly," and over several years. Most families (84 per cent) shared the care of the child with the "intimate family" only. The incidence (16 per cent) of use of "baby-sitters" seems to be fairly low, and may express anxiety also. However, the impossibility of a control group for this point renders our conclusion speculative. If these are expressions of anxiety in depth, they are entirely compatible with the belief held by 32 per cent of the families that the child "might suddenly die"—an unusual mode of exitus for children with congenital heart disease.

The adjustment of the family was enquired after in the sense of over-all improvement, or otherwise, in nonsexual marital relationships. Most (62 per cent) thought that things were the same; 21 per cent thought that relationships were better, and the rest thought that they were worse. When asked to relate these changes to the disease, no very different result was obtained, although 18 per cent thought that the disease had worsened the relationships between man and wife.

Most patients had siblings, and questions were asked to learn whether they had been affected in any way. Thirty-eight per cent said "yes"; of this 38 per cent, "worry" in the sibling(s) occurred in 18 per cent, "hostility" to and "jealousy" of the patient in 10 per cent, "deprivation feelings" in the sibling in 3.2 per cent, and spoiling of the patient by a sibling in 4.4 per cent. Miscellaneous, indefinable reactions occurred in the small remainder.

An effort was made to learn whether various aspects of family life, such as economics, vocational opportunities, social habits, and parental health, had been affected by the disease. On a purely subjective basis, 65 per cent of the group said "yes." These changes were mostly economic, impaired parental health, and limitation of social activities. Only 3 per cent of the group, however, experienced changes in all three categories.

A total reaction to these problems is to be expected; this we called "the adjustment," i.e., a reasonable acceptance of the situation, with understanding of what it implies for the future of the child and the family. "Adjustment," as thus shortly defined, was claimed in 86 per cent of the families. In some, it was a tenuous adjustment at best. A total inability to adjust or accept at any level was found in the others. As to the question of what helped them to achieve adjustment, the replies placed the physician well ahead (56 per cent), and "living with the situation" was next (8 per cent); religion and relatives helped another 5 per cent, and the others, up to a total of 86 per cent, had other resources, such as reading and financial help.

When questioned as to their feelings after "adjustment" was present or absent, 35 per cent still expressed fear; "confidence" was expressed in 37 per cent, "pity," "disgust," and "acceptance" in 4 per cent, "relief" (found only in the postsurgical patients) in 9 per cent, and "guilt" in 4 per cent. Finally, "ignorance" was still present in about 10 per cent. This hardcore had resisted at least two explanations by the pediatrician, illustrative perhaps of the problem of communication which exists even after adequate "rapport" has apparently been achieved.

At a later stage in the illness, at least 6 months after the initial interview, we again tried to assess their feelings about the future—in general terms, including that of the child. When asked directly, 54 per cent expressed "confidence," and 30 per cent were "fearful"; the remainder were unable to give an opinion. These latter probably expressed fear rather

Arrhythmias after cardiac surgery. I. Uncomplicated atrial septal defect

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It is generally recognized that cardiac arrhythmias occur frequently in connection with thoracic surgery, particularly when the heart is involved. Recent spectacular strides in cardiac surgery have succeeded in bringing the risk and morbidity from open-heart surgery to the point where this type of operation compares favorably with average major surgical procedures. Thus, arrhythmias may become bothersome complications which interfere with the usual rapid recovery of the patient after cardiac surgery. A rational approach to the problem of prevention and treatment of such arrhythmias has to depend on a thorough knowledge of all factors involved in their production. It is believed that this end can best be achieved by examining series of cases which are homogeneous with regard to the anatomic abnormality and surgical repair. Such information is not now available since only crude, all-inclusive observations on the incidence of arrhythmias have hitherto been reported. The purpose of this communication is to report an analysis of arrhythmias in patients who underwent surgical repair of the uncomplicated atrial septal defect of the secundum type. A similar study of other lesions is being prepared.

Material and methods

This study was based on a series of 146 patients with the "secundum" type of atrial septal defect who underwent surgical correction at Stanford University Hospitals in San Francisco and its successor, the Presbyterian Medical Center. Nineteen patients had their defect closed by a modification of the Sondergaard external suture technique[1] prior to March, 1957. One hundred and twenty-seven consecutive patients underwent open-heart operation with the aid of extracorporeal circulation between March, 1957, and May, 1961. These two groups were analyzed separately, for purposes of comparison. Partial anomalous venous drainage was present in 23 of these patients, with one or two pulmonary veins entering the superior vena cava or right atrium. These were included in the series as variants of the simple atrial septal defect. The diagnosis of the

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pregnancy." The physician will not lose his intellectual integrity by such a statement, and the parents are not the best people upon whom to extrapolate the latest findings "in the literature."

Most people can cope with the expected; surprises are hard to handle. Therefore, tell them something of the natural history of the disease; this should relieve some of the potential anxiety. Respiratory infections are common in all types of congenital heart disease· warn the parents of this possibility, emphasizing that these infections respond to correct treatment. Many parents will have observed the impairment of growth which is common in the child with congenital heart disease. This retardation will continue until after successful surgery, and the parents should be so informed. Soften the statement, however, by adding, "He will not be dwarfed."

The child with congenital heart disease should be encouraged to be as active as his condition allows. Restrictions will be taken as evidence of insecurity in the physician (as it usually is), and will be contrasted with his verbal optimism. Rational parents will draw the logical conclusion. At the time when the parents are advised concerning the activity of the affected child, the "sibling problem" should be aired. The parents should be advised to give some explanation to brothers and sisters, and to tell them that an overprotective attitude is inappropriate.

The interview must conclude with the statement from the physician, "Do you have anything to ask me now?" This is a salutary question, which often reveals the failure of what sounds like an immaculate explanation. It fails because the parents just cannot comprehend all the implications. Repeat the explanation, and urge them to see their own doctor, who must be *rapidly* briefed as to the findings and opinions of the consultant.

Later visits will sometimes indicate the need for further explanations. The physician need not be surprised to find, for example, that the parents attach more importance to "undue sweating" than to "paroxysmal dyspnea" in a case of inoperable cyanotic heart disease. A gentle but vague reorientation is then advisable. Similarly, as rapport grows, enquiry should be made as to whether the social or other aspects of family life are suffering because of irrational anxieties or beliefs. Again, explanation and re-emphasis may set the situation straight.

The question of cardiac catheterization and angiocardiography occasionally causes confusion. Thus, if parents are told that an anesthetic is necessary, some will jump to the conclusion that the procedure is "curative," and not "diagnostic." They should be left with no illusions concerning this. It has been seen that the possibility of surgery is usually well received; potential refusal of operation is prevented by adequate explanation of what is hoped for by surgery. As always, complete frankness in all aspects is necessary, both by physician and surgeon; the final decision for surgery should be made by the parents in their own environment, and not in the hospital clinic.

All members of the cardiological team must share the same attitudes. Thus, all trainees must be orientated early as to the general line of explanation and action practiced by any particular clinic. Thus is avoided the difference of opinion which, although medically minor, may become major to an anxious parent.

It is not claimed that this protocol is exhaustive. However, if these few points are covered, perhaps much anxiety may be relieved. Explanation and guidance are the ways by which the physician maintains his claim to "help the family adjust."

Summary

A pilot study has been made of the effect of a child with congenital heart disease upon his family. Many aspects of family life are found to be affected, and feelings and reactions of insecurity are common in parents and siblings; failure of adjustment occurs in 14 per cent of all families.

A simple scheme for the prevention of some of these difficulties is outlined.

any medication. Atrial flutter and fibrillation were present preoperatively in 4 of the 19 patients who had these arrhythmias postoperatively. Of the other 15 patients, 8 developed their arrhythmia sometime after the sixth postoperative day—one patient as late as 6 weeks after the operation. Nine developed atrial fibrillation during the first 5 days. In 12 of these 15 patients the rhythm was eventually converted to sinus rhythm, although in some cases several attempts at conversion were necessary.

Preoperative cardiac catheterizations were also reviewed in relation to pulmonary arterial pressures, and a systolic pres-

Table III. Incidence of arrhythmias in relation to age of the patient

Age (yr.)	*Number of cases*	*Patients with benign arrhythmias*		*Patients with serious arrhythmias*		*Number with arrhythmias*	
0–8	35	10	28%	0	0	10	28%
9–17	41	13	32%	1	2%	14	34%
18–26	19	5	26%	4	21%	9	47%
27–35	15	4	26%	4	26%	8	53%
36–45	9	1	12%	5	56%	6	66%
46–55	8	1	13%	7	87%	8	100%

Table IV. Cardiac rhythm in patients with pulmonary hypertension

Age (yr.)	*Rhythm*	*Pulmonary arterial pressure (mm. Hg)*
6	A-V dissociation	60/28
9	Nodal tachycardia	65/22
19	Sinus rhythm	73/46
19	Nodal rhythm	63/80
25	Atrial fibrillation	69/78
25	Sinus rhythm	103/41
25	Sinus rhythm	81/40
46	Atrial fibrillation	76/28
46	Atrial fibrillation	100/60
49	Atrial fibrillation	76/32

Table V. Effect of various forms of surgical procedures on arrhythmias

	Sinus rhythm	*Arrhythmias*	*Total*
A. *Variation in technique in open-heart surgery*			
Average length of perfusion	23 min	30 min.	26 min.
Patients with 2 separate incisions for cardiac cannulation	12 (16%)	13 (24%)	25 (20%)
Use of hypothermia (31°–28°C)	43 (60%)	44 (80%)	87 (68%)
Use of a patch in repair of defect	12 (17%)	11 (20%)	23 (18%)

	Closed techniques	*Open techniques*	*Total*
B. *Closed-heart versus open-heart operation*			
Number of cases	19	127	146
Arrhythmias	9 (47%)	55 (43%)	64

Table I. Total number of arrhythmias encountered in the series

Arrhythmia	*Total number of arrhythmias*	*Major type in each patient*
Nodal rhythm	33	25
Second-degree heart block	3	1
A-V dissociation	10	8
Supraventricular tachycardia	4	2
Atrial flutter with varying block	10	6
Atrial fibrillation	13	13
	73	55

Table II. Arrhythmia and sex distribution

	Males	*Females*	*Total*
Total number of patients	44 (35%)	83 (65%)	127 (100%)
Arrhythmias	17 (31%)	38 (69%)	55 (43%)

lesion was based on preoperative cardiac catheterization in every case, and surgical exploration of the right atrium.

Every patient had a complete electrocardiogram prior to operation, and on the day before discharge from the hospital, approximately 10 days after the operation. For the first 3 postoperative days, partial electrocardiograms (rhythm strips) were taken daily, and, frequently, additional tracings were recorded. All these studies were reviewed by the authors.

Pertinent details of surgical technique were noted. These included the type of incision, use of a prosthetic patch, incidence and degree of hypothermia, and length of body perfusion.

Results

Fifty five of one hundred and twenty-six patients (43 per cent) who underwent open-heart operation developed an arrhythmia. There was a total of 73 arrhythmias, indicating that many patients had more than one type. The incidence of the most persistent or bothersome arrhythmia in each patient is shown in the right-hand column of Table I.

Analysis for sex and age is shown in Tables II and III, respectively. There were twice as many females as males in the group as a whole, and this ratio remained the same in the groups with and without arrhythmias. Thirty-two per cent of the patients in the age group 0-17 years, and 60 per cent in the group 18-55 years, had arrhythmias. This trend of greater incidence after 17 years of age is statistically significant; the probability is less than 1 per cent that this variation could have occurred by chance, $p < .01$.

Arrhythmias were arbitrarily divided into "benign" and "serious." The former included nodal rhythm and A-V dissociation which did not require treatment, and the latter included atrial tachycardias, flutter, and fibrillation.

When nodal rhythm occurred, it presented itself nearly always immediately after the operation, and 18 of 25 patients were in sinus rhythm at the time of discharge from the hospital. Seven patients still had nodal rhythm, and in 2 this persisted 1 year later. It has not been possible to obtain tracings on the other 5 patients. A-V dissociation, as the most serious arrhythmia in a patient, also presented itself in the immediate postoperative period. In 7 of these 8 patients the reversion to sinus rhythm was spontaneous between the third and eleventh days after operation. The eighth patient still had dissociated rhythm 1 year later, but had a ventricular rate of 90 per minute without the need for

Table VI. "Serious" atrial arrhythmias in postoperative period after atrial septal repair

Name	Age (yr)	Sex	Cardiomegaly	Pulmonary hypertension	Type of arrhythmia	Onset (after operation)	Duration	Recurrence	Treatment	Remarks
P.L.	16	M	0	0	A F.	3rd day	4 hours	0	0	
D.S.	19	F	+	0	A.F.	2nd day	1 day		Digitalis	First attack
					A F.	14th day	10 days	1	Quinidine	Second attack
R.V.	19	F	0	0	A.F.	23rd day	8 days	0	Digitalis	Onset of A.F. preceded by thrombophlebitis
C.T.	25	F	+	+	A Fl.	9th day	2 days	2	Digitalis	First attack
					A.T.	62nd day	10 days		Quinidine	Second attack
S E.	28	F	0	0	A.Fl	5th day	4 hours	0	0	
E.W.	31	F	0	0	A.Fl	16th day	2 days	0	Digitalis	
K G.	32	F	+	0	A.Fl.	9th day	1 day	1	Quinidine	First attack
					A.Fl.	11th day	8 days		Quinidine and digitalis	Second attack
V.W.	40	F	+	0	A F A.Fl	2nd day 3rd day	14 days	0	Digitalis and quinidine	First attack Second attack
F.D.	41	F	0	0	A F	2nd day	Few hours	1	Digitalis	
						4th day	Few hours			
A.A.	42	F	++	0	A Fl	2nd day	3 days		0	Paroxysmal A.F. before operation
					A Fl.	42nd day	Permanent		Digitalis and quinidine	
G.C.	42	M	0	0	A.Fl.	4th day	7 days	2	Digitalis and quinidine	
E.D.	43	F	+	0	A F.	4th day	3 days	0	Digitalis	
M.D.	46	F	++	+	A.T.	6th day	5 days	2	Digitalis and quinidine	
R.C.	46	F	+	+	A F.	1st day	Died on 3rd day		Digitalis	A.F. prior to operation
W.S.	47	M	0	0	A.F.	11th day	6 days	2	Quinidine	Paroxysmal A.F. before operation
					A.Fl , A.T	23rd day	6 days		Digitalis	
T.D.	49	F	+	+	A F., A.Fl.	1st day	Permanent		Digitalis and quinidine	Paroxysmal A.F. and A.Fl. before operation
V.B.	51	F	+	0	A.Fl.	2nd day	3 months		Quinidine Digitalis	A Fl. repeatedly prior to operation
W.H.	53	F	0	0	A F.	10th day	2 days	0	Digitalis	
C.B.	55	F	+	0	A.F.	6th day	2 days	0	Digitalis	

A.F : Atrial fibrillation. A.Fl : Atrial flutter. A.T.: Atrial tachycardia.

sure of 60 mm. Hg or more was considered to be a definite indication of significant pulmonary hypertension. Table IV shows an analysis of these patients in respect to the incidence of arrhythmias. A total of 10 patients (8 per cent) fall into this category.

Table V is concerned with various surgical techniques. Two separate incisions into the right atrium did not influence arrhythmias. A patch was necessary in 19 patients, and was used relatively more often in the older age group. However, this did not increase the incidence of arrhythmias in that group appreciably. The average length of perfusion did not vary a great deal. Hypothermia (28 to 31 degrees centigrade) was used in 87 patients (68 per cent of this series), and has been used regularly since June, 1959. The incidence of arrhythmias is slightly higher in this group, but this is not statistically significant. With the "closed" technique, 9, or 47 per cent, had an arrhythmia, which shows that the incidence was the same as in the "open-heart" group, and the distribution of benign and serious arrhythmias in the two groups was fairly even.

Table VI lists the details in 19 cases in which atrial tachycardia, flutter, and fibrillation developed after the operation. In these cases it is noteworthy that (a) all but 2 patients required therapy; (b) there was a tendency toward recurrence of the arrhythmia, with the recurrent attacks more resistant to therapy than the initial ones; and (c) the development of these arrhythmias appears to be unrelated to the hemodynamic derangement as judged by the presence or absence of cardiomegaly and pulmonary hypertension.

Discussion

Atrial septal defect is one of the most common congenital cardiac lesions, and its closure has become a safe operative procedure in most surgical cardiac centers. The mortality has decreased significantly in the last 5 years, and in our series there was no death in the last 97 cases. However, occasional arrhythmias, especially in the older age group, have complicated the otherwise smooth and rapid postoperative course.

As already stated, arrhythmias encountered in this series were divided into benign and serious types. In the former, nodal rhythm and atrioventricular (A-V) dissociation were included. These two rhythms accounted for virtually all arrhythmias found in children. Nodal rhythm, which as a rule developed in the immediate postoperative period, led to no subjective symptoms or circulatory embarrassment. This is presumably due to the fact that the nodal pacemaker maintained a resting rate, and responses to exercise were close to normal. As a rule, sinus rhythm was established spontaneously. In the rare instances in which nodal rhythm persisted, it was considered to be an unimportant variant of cardiac rhythm. A-V dissociation was included in the benign group of arrhythmias because of its transient nature after closure of the atrial septal defect. This stood in marked contrast to the traumatic A-V block which has been observed in connection with other forms of cardiac surgery. A-V dissociation also occurred in the immediate postoperative period, and, with one exception, reverted spontaneously to a sinus rhythm. In some patients this did not occur until 9 or 10 days after the operation; the electrocardiogram first showed second-degree heart block, and, later, first-degree heart block before sinus rhythm was established. Heart failure has not been present in this group of patients. However, on the basis of our experience with patients who did have this arrhythmia and became decompensated after total correction of tetralogy of Fallot or interventricular septal defect with elevated pulmonary arterial pressure, we believe that careful digitalization is not contraindicated. Rabbino,[2] in his paper reviewing 211 patients, mentions 14 cases of atrial septal defect; 4 of these 14 patients had subsequent arrhythmias, including transient A-V dissociation. He also thinks that digitalis does not have to be withheld on account of this arrhythmia.

The serious types of arrhythmias required drug therapy in most cases. On the average, supraventricular tachycardia, atrial flutter, or atrial fibrillation developed later than the benign arrhythmias. Frequently, recurrences took place, causing subjective discomfort and signs of circulatory embarrassment due to a rapid ven-

so that only 9 patients had been given this drug prior to the operation—in all of them because of pre-existing cardiac failure or atrial fibrillation. All such patients were over 30 years of age. Six of them developed "serious" atrial arrhythmias, a percentage comparable to the remainder of the series in this age group. No other drugs were used consistently before or after operation.

The practical importance of our findings is twofold. In the first place, the frequency of serious atrial arrhythmias in adults is emphasized. In the second place, the relative refractoriness of these arrhythmias to therapy and their tendency to recurrence is apparent. Because of this it is highly improbable that prophylactic administration of either digitalis or quinidine would reduce the frequency of postoperative arrhythmias. It is generally believed that repair of atrial septal defect is indicated in childhood, even in asymptomatic patients, provided that minimum-risk facilities are available for such operations. The principal reason for this belief is the occasional development of secondary pulmonary vascular changes in adults, which can render some cases inoperable because of shunt reversal. The frequency and persistence of atrial arrhythmias reported in this study are offered as an additional argument in favor of early closure of atrial septal defects.

Summary and conclusion

In 146 consecutive patients who underwent surgical repair of uncomplicated atrial septal defects of the secundum type, the frequency of the various postoperative arrhythmias has been studied and correlated with various predisposing and precipitating factors. Arrhythmias were divided into innocent (nodal rhythm and temporary atrioventricular dissociation) and serious (nonparoxysmal supraventricular tachycardias, atrial flutter, and atrial fibrillation).

The total incidence of arrhythmias in this series is 43 per cent. The age of the patients was found to be the most important factor involved in the development of arrhythmias: the total incidence of arrhythmias increased from 28 per cent in the youngest to 100 per cent in the oldest age group. The frequency of benign arrhythmias fell from 28 per cent in the youngest to 13 per cent in the oldest age group; that of serious arrhythmias increased from 0 to 87 per cent in the comparable groups. The serious arrhythmias not only appeared in the majority of adult patients, but showed a tendency to recurrences and refractoriness to therapy.

Age was found to be the only clear-cut predisposing factor. Other factors, such as pre-existing pulmonary hypertension, cardiomegaly or cardiac failure, did not appear to have a direct relationship to the frequency of postoperative arrhythmias. The precipitating factor is presumed to be the surgical trauma to the heart, or its sequelae. Technical variations, such as the use of the closed method versus the open method of repair, the use of hypothermia versus body temperature, the length of perfusion, and the use of prosthetic material, had no detectable influence upon the arrhythmias.

Atrial arrhythmias are shown to be significant complications which increase the morbidity and prolong the hospitalization of adult patients who undergo such cardiac surgery. Therefore, further weight is added to the view that the optimal time for closure of atrial septal defect is in the age bracket of childhood.

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tricular rate. It is noteworthy that ventricular arrhythmias have not been encountered in our series.

In the analysis of the factors responsible for the arrhythmias it is necessary to consider separately the predisposing and the precipitating factors. Among the former, two factors deserve comment: the age of the patient and the severity of circulatory derangement. The increase in the incidence of arrhythmias with age (Table III) appears to be the most striking finding of our study. This increase is entirely accounted for by the almost exclusive occurrence of the "serious" arrhythmias in adults and the higher frequency of these arrhythmias with advancing age of the patients. Among the innocent arrhythmias, nodal rhythm occurred with comparable frequency in children and adults, and A-V dissociation occurred rarely in adults. In a review of 58 children under 14 years of age who had their atrial septal defects closed by the atrial-well technique, McGoon and co-workers[3] also mention only nodal rhythm and A-V dissociation postoperatively. Thus, age appears to be an important predisposing factor for the development of atrial arrhythmias in general, as shown by the occurrence of these arrhythmias in 4 of our patients prior to the operation, and by the findings of other investigators—Davidsen[4] and Rodstein.[5] Davidsen not only stresses the occurrence of atrial arrhythmias in the older patient, but also ascribes to them an unfavorable prognosis. The fact that drug therapy permitted the permanent restoration of sinus rhythm in nearly all our patients demonstrates the favorable influence of atrial septal repair in the control of the arrhythmia.

An assessment of the influence of the severity of the circulatory derangement upon arrhythmias was made through two approaches: (1) the cardiac rhythm was examined in patients with pulmonary hypertension (Table IV); and (2) the incidence of cardiac enlargement and of pulmonary hypertension was determined in patients with serious arrhythmias (Table VI). Using a systolic pulmonary arterial pressure of 60 mm. Hg or more, we found that 10 patients in our series had pulmonary hypertension. Although the small number of cases in these two tables precludes a statistical evaluation, it is evident that patients with pulmonary hypertension, which is the most important additional circulatory overload in atrial septal defect, do not always develop atrial arrhythmias. Furthermore, a reasonable number of patients with atrial arrhythmias do not show cardiomegaly or pulmonary hypertension. These findings suggest that the severity of the circulatory derangement is not of prime importance as a predisposing factor for the production of arrhythmias.

There is little doubt that thoracic surgery alone constitutes a major precipitating factor in the production of atrial arrhythmias, since an appreciable incidence of such arrhythmias has been reported in pulmonary[6,7] and esophageal[8] surgery, particularly in older individuals. In Table V, various surgical aspects have been examined as possible precipitating factors. The magnitude of surgical trauma as measured by the total length of perfusion, the use of a prosthetic patch, or additional incisions for cardiac cannulation do not materially alter the susceptibility to arrhythmias. Similarly, there was no appreciable difference whether the repair was made with the aid of extracorporeal circulation (open technique) or by the external suture technique (Table V,*B*). The use of hypothermia also does not seem to have a statistically significant effect on the incidence of arrhythmias. The possibility of electrolyte disturbances has been considered. As has been stated, the majority of the serious arrhythmias did not develop until after the second day, by which time the patient was starting to eat a regular diet. In our patients, we have found that the serum pH, pCO_2, and electrolytes were normal at this time. The general conclusion appears to be justified that surgical manipulation of the atrium constitutes a more potent arrhythmogenic factor than does other thoracic surgery, but that other technical considerations play no important role in the production of the atrial arrhythmias.

The administration of drugs as another precipitating factor was also considered. Prophylactic administration of digitalis is not part of the routine in this institution,

some anticoagulant, but their course of therapy was too short to accurately assess the value of anticoagulant therapy. The 484 patients who remained became the basis of this study.

On the basis of anticoagulant control, each of the 484 patients was placed in one of the following groups (Table I): *Group A:* Those with a therapeutic range of 10 to 30 per cent prothrombin activity. All of these were in this range within 4 days of the institution of anticoagulant therapy and remained so for a minimum of 70 per cent of the period of hospitalization. *Group B:* Those with a therapeutic range of 10 to 40 per cent prothrombin activity. Criteria for this group were otherwise identical with those of Group A. *Group C:* Those who received anticoagulant therapy for the entire period of hospitalization but failed to meet the criteria for either Group A or Group B. *Group D:* Those who did not receive any anticoagulant drugs.

A modified Quick one-stage prothrombin time determination, with either Solu-Plastin* or Simplastin† as the thromboplastin source, was used to measure anticoagulant effect.[8] Solu-Plastin, with a control time of 15 seconds, was used as the thromboplastin source for the first 8 months of this study; for the remaining 16 months, Simplastin, with a control time range of 11.8 to 12.5 seconds, was used.

Results

Mortality rate. In Group A there were 168 patients, with 16 fatalities, a mortality rate of 9.5 per cent. Among the 196 patients in Group B there were 6 fatalities, a mortality rate of 3.1 per cent. There were 6 fatalities among the 81 patients in Group C, a mortality rate of 7.4 per cent. In Group D there were 39 patients with 8 fatalities, a mortality rate of 20.5 per cent. Thus, the mortality rate in Group A, the group with rigid anticoagulant control, was considerably higher than that in Group B, the group with moderate control. The mortality rate in Group A was also slightly higher than that in Group C, in which the control was poor. The mortality rate in all groups which received anticoagulant therapy was substantially lower than that in Group D, in which no anticoagulant therapy was given. (See Table II.)

Because the mortality rate in acute myocardial infarction is influenced by many factors, the true effect of anticoagulant therapy is often difficult to determine. Therefore, the groups were analyzed for the following factors which are known to affect mortality rate[1-4]: (1) age, (2) associated heart failure, (3) shock, (4) arrhythmias and conduction defects, (5) previous myocardial infarctions, (6) preinfarction heart failure, (7) hypertension, (8) diabetes mellitus, (9) uremia, and (10) obesity. There were no cases of uremia. The available data were not sufficient to determine the incidence of obesity. The results of the study were submitted to chi-square analysis in order to determine whether there was any statistically significant variation in the incidence of any of these other factors between the four groups. (See Table II.)

The difference of approximately 9 years in average age between the patients of Group C and those of the other three groups prevented any comparison of mortality rates. The higher incidence of associated heart failure, arrhythmias, and conduction defects in Group D obviated any comparison between it and the other groups. The only significant difference between Group A and Group B was the greater percentage of patients over the age of 60 years in Group A. However, further analysis revealed that there was still a significantly higher mortality rate in Group A in patients over the age of 60 years. The mortality rate for patients over 60 years of age in Group A was 12.5 per cent, whereas in Group B it was 4.2 per cent. For patients who were under the age of 60 years in these two groups the mortality rates were not significantly different. (See Table III.)

The mortality rates which were associated with these various factors were also studied. This revealed that: (1) there was a significantly higher mortality rate associated with congestive heart failure in Group A, and (2) although the differences were not statistically significant, there

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Anticoagulant control in acute myocardial infarction

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Within the past 10 years, anticoagulant therapy has played an increasingly important role in the treatment of acute myocardial infarction. It has been well established that anticoagulant therapy reduces the incidence of thromboembolic complications.[1-4] Additional work strongly suggests that the incidence of recurrent myocardial infarction is appreciably reduced by anticoagulant therapy.[3,5-7] Some investigators report beneficial results in the treatment of impending myocardial infarction when anticoagulant therapy is administered.[8]

As is the case with any new type of therapy, certain problems associated with its use arise Among the problems associated with the use of anticoagulant therapy are: (1) uncertainty in regard to the necessary degree of depression of the prothrombin time (the therapeutic range), and (2) the risk of hemorrhage.

This study was undertaken to determine what relationships exist between anticoagulant control and mortality rate, thromboembolic complications, and hemorrhagic complications in acute myocardial infarction.

Materials and methods

Five-hundred and seventy-two patients with acute myocardial infarction were admitted to Mount Carmel Mercy Hostal from Jan. 1, 1959 to Dec. 31, 1960. Criteria for the diagnosis of acute myocardial infarction were either diagnostic serial electrocardiographic changes, or electrocardiographic changes which were compatible with this diagnosis and were supported by a characteristic clinical picture and typical changes in serum enzymes.

Eighty-eight patients were eliminated from the study because they failed to survive the initial 4 days of hospitalization. Fifty-six of these died before receiving anticoagulants. Thirty-two received

Table I

Group	*Therapeutic range*	*Control*
A "Rigid" control	10 to 30%	Prothrombin time in the therapeutic range within 4 days of institution of anticoagulant therapy and remaining there for at least 70 per cent of the period of hospitalization
B "Moderate" control	10 to 40%	
C	—	Received anticoagulant therapy for entire period of hospitalization but did not meet criteria for either Group A or Group B
D	—	Received no anticoagulant therapy

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curred while the patient was under treatment in the hospital for acute myocardial infarction. (See Table IV.) Among the patients of Group D there was only one thromboembolic complication, a nonfatal pulmonary embolus. Because of the disparity in size, Group D was thought not to represent an adequate control group. There were 11 thromboembolic complications in Group A, 9 of which were extensions of myocardial infarction. In Group B there were 16 thromboembolic complications, 11 of which were extensions of myocardial infarctions. In each of these groups 2 of the extensions were fatal. The variation in the incidence of thromboembolic complications between Group A and Group B was insignificant, being 6.5 and 7.1 per cent, respectively. The mortality rates attributable to thromboembolic complications also varied slightly, being 1.2 per cent in Group A and 1 per cent in Group B. In Group C there were 4 thromboembolic complications, including one fatal pulmonary embolus, an incidence of 4.9 per cent and a mortality rate of 1.2 per cent.

The incidence of thromboembolic complications can be considered to be a better indication of the effectiveness of anticoagulant therapy than mortality rate because it is influenced by fewer factors. However, it is known that a significant number of thromboembolic complications occur without apparent clinical recognition.[16] Thus, the accuracy of this method of assessing the effectiveness of anticoagulant therapy is doubtful The results with both methods, mortality rate and thromboembolic complications, however, are in agreement that moderate anticoagulant control is associated with results that are equal to, or better than, the results obtained with rigid anticoagulant control.

Hemorrhagic complications. The onset of spontaneous bleeding while anticoagulants were being administered was regarded as a hemorrhagic complication unless another specific etiological factor was identified There were 13 episodes of unexplained spontaneous bleeding in Group A, and 15 such episodes in Group B, an identical incidence of 7.7 per cent in each group. In Group C there were 7 episodes of unexplained spontaneous bleeding, an incidence of 8.6 per cent. None of these episodes of bleeding was fatal. The most common sites of bleeding were the genitourinary and gastrointestinal tracts.

The patients of Groups A, B, and C who had hemorrhagic complications were further studied for prothrombin activity at the time of bleeding. Of the total of 34 episodes of bleeding in all three groups, 13 occurred when the prothrombin activity was less than 10 per cent; in an additional 11 cases, spontaneous bleeding occurred when the prothrombin time was between 10 and 20 per cent, and in the other 10 cases of hemorrhagic complications the prothrombin activities ranged between 22 and 70 per cent. Two of the patients who had prothrombin activities above 40 per cent were receiving heparin at the time of onset of bleeding. Thus, in 24 of the 34 cases (68.6 per cent), bleeding was associated with prothrombin times of less than 20 per cent.

Discussion

One might question the use of the terms *rigid* and *moderate* as applied in this study. The difference between 30 per cent and 40 per cent prothrombin times represents a difference of 1 to 4 seconds in the end point of the modified Quick one-stage prothrombin determination. As shown by this study, this difference of 1 to 4 seconds is not a critical point in the in vivo hypocoagulability, in so far as prevention of intravascular thrombosis in acute myocardial infarction is concerned. Of greater importance is the increased risk of the complications of hemorrhage which is associated with depression of the prothrombin time to levels below 20 per cent. The unreliability of the modified Quick one-stage prothrombin time at these levels

Table V

Prothrombin activity at time of bleeding	*Patients with hemorrhagic complications*
Less than 10%	13
10%—20%	11
20%—40%	7
Above 40%	3

Table II

Group	*A*	*B*	*C*	*D*
Total cases	168 (16)	196 (6)	81 (6)	39 (8)
Mortality rate	9 5%	3.1%	7.4%	20.5%
Average age (yr.)	64	63.2	55.2	64.3
Patients over age 60 years old	96 (12)	95 (4)	30 (5)	28 (7)
Associated heart failure	43 (11)	42 (3)	13 (4)	15 (7)
Shock	7 (3)	8 (1)	3 (0)	3 (1)
Arrhythmias and conduction defects	36 (5)	37 (3)	18 (3)	13 (4)
Previous infarctions	37 (3)	49 (2)	19 (2)	16 (2)
Preinfarction heart failure	17 (4)	17 (1)	2 (1)	6 (3)
Hypertension	26 (4)	29 (0)	13 (0)	7 (1)
Diabetes mellitus	19 (1)	18 (1)	11 (1)	8 (2)

Parentheses indicate fatalities.

Table III

	Group A		*Group B*	
	Total	*Fatalities*	*Total*	*Fatalities*
Over age 60 years	96 (57.1%)	12 (12.5%)	95 (48.4%)	4 (4 2%)
Under age 60 years	72	4 (5 5%)	101	2 (1 9%)
Total cases	168	16 (9.5%)	196	6 (3.1%)

Table IV

Group	*A*	*B*	*C*	*D*
Thrombophlebitis	1	3	1	0
Pulmonary embolus	1	1	2 (1)	1
Systemic embolus	0	1	1	0
Extension of myocardial infarction	9 (2)	11 (2)	0	0
Totals	11 (2)	16 (2)	4 (1)	1 (0)
Incidence	6.5%	7.1%	4 9%	2 6%
Mortality rate	1 2%	1.0%	1 2%	0%

Parentheses indicate fatalities.

was a trend which indicated a consistently higher mortality rate associated with each factor in Group A.

In summary, then, although the relative incidences of the factors which affected the mortality rate were not significantly different between Group A and Group B, the data suggest that the degree of severity of each factor was. This would account in part at least for the higher mortality rate in Group A. Of greatest importance, however, was the finding that, in so far as mortality rates were concerned, the results obtained with moderate anticoagulant control were at least equal to, if not better than, those obtained with rigid anticoagulant control.

Thromboembolic complications. Included as a thromboembolic complication was any episode of thrombophlebitis, pulmonary embolus, systemic embolus, or extension of myocardial infarction which oc-

Secundum atrial septal defects with congestive heart failure during infancy and early childhood

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Atrial septal defects of the ostium secundum type are generally not considered to be a cause of morbidity and death in infancy and early childhood. Rare instances of these complications have been included in some of the larger autopsy and clinical series on atrial septal defects,[1-7] but the emphasis has been on the favorable prognosis. The older literature is particularly difficult to evaluate because of the lack of differentiation between ostium primum and ostium secundum defects.

Recently, we have been impressed by the appearance of severe congestive heart failure in several infants with uncomplicated atrial septal defects of the secundum type. This report deals with 13 cases in which congestive heart failure in infancy and early childhood was a cause of morbidity or death. Seven cases were obtained from a review of our autopsy files since 1945, and six from the catheterization files from 1958 through 1961.

Clinical, physiologic, and autopsy data

Table I summarizes the clinical course and physical findings.

The age of onset of symptoms extended from birth to 1½ years; however, only 3 patients were older than 6 months. A history of frequent or chronic respiratory infection was always noted. Most infants had had dyspnea and tachypnea for several weeks or months prior to examination at our clinic, and were referred because of a progressive increase in symptoms or an acute exacerbation of symptoms. Congestive heart failure was manifest by the presence of dyspnea, tachypnea, tachycardia, cardiac enlargement, and hepatomegaly, and, in most cases, gallop rhythm and peripheral edema. The frequent finding of basal pulmonary râles was difficult to evaluate because of the common occurrence of associated respiratory infection.

The cardiovascular physical findings in this group were quite uniform. A right ventricular systolic impulse was present at the lower left sternal border or xiphoid area. The first heart sound was normal. The second heart sound had a normal or slightly increased intensity at the upper left sternal border and was usually widely split and fixed with respiration. A Grade 2 to 4 systolic ejection murmur was heard best at the

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in particular has been reported.[11] Furthermore, the results of this study did not reveal any increased effectiveness of anticoagulant therapy at these lower levels. It is suggested, therefore, that the ideal therapeutic range for anticoagulant therapy in acute myocardial infarction is between 20 and 40 per cent when the modified Quick one-stage prothrombin time is used to measure anticoagulant effect.

Summary

An analysis of 484 cases of acute myocardial infarction was undertaken to determine relationships which exist between anticoagulant control and mortality rate, thromboembolic complications, and hemorrhagic complications. On the basis of anticoagulant control, the cases were assigned to various groups. A comparative study of mortality rates revealed that the results obtained with moderate anticoagulant control were equal to, or better than, the results obtained with rigid control. There was no significant difference in the incidence of thromboembolic complications between the rigidly and moderately controlled groups. The mortality rates associated with thromboembolic complications also varied little between these groups. Hemorrhagic complications were frequently associated with prothrombin times below 20 per cent. A therapeutic range of 20 to 40 per cent using the modified Quick one-stage prothrombin time should: (1) favorably influence the mortality rate in acute myocardial infarction, (2) provide adequate protection against thromboembolic complications, and (3) significantly minimize the risk of hemorrhagic complications.

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Table II lists the important radiologic and electrocardiographic findings. The chest x-ray films in all cases showed moderate to marked cardiac enlargement and increased pulmonary vascular markings. In most instances there was a prominent pulmonary artery segment. During the periods of cardiac failure the heart became larger in size and there was also passive pulmonary congestion (Fig. 1). The heart reverted rapidly to its original size after anticongestive treatment. The electrocardiographic data (Fig. 2) showed a mean QRS axis of +90 to 120 degrees, with two exceptions. In one of these the axis was indeterminate, and in the other, −150 degrees. Four patients had a first-degree atrioventricular block, which is in accord with previously reported findings in cases of atrial septal defect. Right atrial hypertrophy was observed in 7 patients. Right ventricular hypertrophy with an rsR′, qR, or, in one case, an Rs pattern in Lead V_1 was present in all our cases. The electrocardiograms were not available for evaluation in 3 of the autopsied patients.

The cardiac catheterization data (Table III) were quite uniform in several respects. In each patient there was a large left-to-right shunt at the atrial level, and no other shunts could be demonstrated. Arterial oxygen saturation was normal. In all instances the right ventricular systolic pressure was between 50 and 60 mm.Hg. In 2 patients there was mild pulmonary hypertension. In the other patients there was a pressure gradient of from 20 to 30 mm.Hg across the pulmonic valve. The atrial septal defect was traversed in all patients, and left atrial and left ventricular pressures were normal and no significant pressure gradients across the mitral valve were observed. The cardiac catheterization data were not available for any of the autopsied patients.

In 4 of the 6 clinical cases, the diagnosis was confirmed by selective cineangiocardiography, including injections into the left ventricle to exclude additional small ventricular septal defects. The diagnosis was confirmed by operation in another (C.M.).

The clinical course followed one of two patterns: (1) Heart failure progressed in severity and resulted in an early death. Death occurred between 3 weeks and 1 year of age, except in 1 patient who died at 3 years of age. The presence of a respiratory infection was considered to be an important contributing factor to mortality. (2) Therapy produced a favorable response, and with advancing age there was progressive clinical improvement. Some of these patients had a definite decrease in heart size later in life.

Table III. Cardiac catheterization findings in 6 infants with atrial septal defect (secundum) who developed cardiac failure

Patient	Per cent oxygen saturation					Pressures (mm Hg)							Pulm. flow*	Syst flow*	Pulm. vasc. res.*
	SVC	RA	RV	PA	FA	RA	RV	PA	LA	LV	FA	PC_w			
L.S.	67	84	84	83	95 0	4	55/5	30/10 M = 12	5	90/0	—	—	11 5	5 5	N
R.L.	67	82	82	84	96	4	50/5	40/15 M = 28	5	90/6	75/45 M = 60	8	9 5	3.5	N
L.M.	44	85	85	86	96	2	52/4	22/10 M = 16	3	110/0	—	—	10 0	2 0	N
S.T.	50	89	85	—	98	6	60/0	21/12 M = 17	7	70/5	90/54 M = 62	—	14.0	3 5	N
J.W.	61	86	83	84	99	3	50/3	52/10 M = 32	5	95/5	—	—	10 0	3 5	N
C.M.	62	89	92	92	98	5	58/2	37/15 M = 20	7	120/5	—	10	17.0	3 5	N

*Estimate based on assumed oxygen consumption of 170 ml./min./M².
SVC Superior vena cava. RA: Right atrium. RV: Right ventricle. PA. Pulmonary artery. FA: Femoral artery LA: Left atrium. LV: Left ventricle PC_w: Pulmonary arterial wedge pressure. *Pulm flow:* Pulmonary blood flow, in L./min./M². Syst flow: Systemic blood flow, in L./min./M². Pulm. vasc. res.: Pulmonary vascular resistance. N: Normal. M: Mean pressure — Data not available.

Table I. Clinical findings in 13 infants with atrial septal defect (secundum) who developed cardiac failure

Patient	Age at onset of symptoms	Age at death	Respiratory infections	Dyspnea	Hepatomegaly	Edema	Gallop rhythm	Thrill (MLSB)	Systolic murmurs (MLSB)	Diastolic murmurs (apex)	Splitting of second heart sound	Studies
P.R.	Birth	3 wk.	Terminal	+	+	+	+	—	—	—	—	P
T.S.	2 wk.	3 wk.	Terminal	+	+	+	+	—	—	—	—	P
R.T.	1 mo.	7 wk.	Terminal	+	+	+	+	—	Grade 2	Grade 2	—	P
B.K.	Birth	6 mo.	Frequent	+	+	+	0	++	Grade 4	Grade 1	Wide	P
E.C.	8 mo.	11 mo.	Once	+	+	+	+	—	—	—	Wide	P
R.A.	1½ yr.	3 yr.	Frequent	+	+	0	+	++	Grade 4	Grade 2	—	P
M.E.	2 mo.	7 mo.	Frequent	+	+	0	+	—	—	—	—	P
L.S.	9 days	0	Occasional	+	+	+	+	+	Grade 3	Grade 2	Wide	C, A
R.L.	Birth	0	Frequent	+	+	0	0	+	Grade 3	Grade 1	Wide	C
L.M.	3 mo.	0	Frequent	+	+	0	+	0	Grade 2	Grade 2	Wide	C, A
S.T.	1 mo.	0	Chronic	+	+	0	0	++	Grade 4	Grade 2	Narrow	C, A
J.W.	5 mo.	0	Chronic	+	+	0	0	0	Grade 3	0	Wide	C, A
C.M.	8 mo.	0	Occasional	+	+	0	0	0	Grade 2	Grade 2	Wide	C, S

MLSB Mid left sternal border P. Postmortem examination. C: Cardiac catheterization. A. Angiocardiography S: Surgery —Auscultatory description not complete.

Table II. Roentgenographic and electrocardiographic findings in 13 infants with artial septal defect (secundum) who developed cardiac failure

Patient	Chest x-ray examination		Electrocardiogram				
	Heart size*	Pulmonary vasculature†	Mean QRS axis	1° A-V block	QRS complex in V_1	RAH	RVH
P.R.	2-3+	2+	−150°	+	qR	0	+
T.S.	2+	1-2+	—	—	—	—	—
R.T.	2+	1-2+	—	—	—	—	—
B.K.	2+	1-2+	+120	0	rsR'	+	+
E.C.	2-3+	2+	+115	0	qR	+	+
R.A.	2+	1-2+	+120	+	rsR'	+	+
M.E.	1-2+	1+	—	—	—	—	—
L.S.	2+	1+	+120	0	Rs	0	+
R.L.	2+	1-2+	+120	+	rsR'	+	+
L.M.	1-2+	1-2+	Indeterminate	0	rsR'	+	+
S.T.	1-2+	1-2+	+ 90	0	Rs	+	+
J.W.	1+	1+	+ 90	0	rsR'	0	+
C.M.	2+	1-2+	+120	+	qR	+	+

*Heart was graded from 1 to 4+

†Pulmonary vascular markings estimated from 1 to 3+.

RAH: Right atrial hypertrophy. RVH. Right ventricular hypertrophy. — Data not available.

upper or mid left sternal border in 9 out of 13 of these patients, and in 5 patients the murmur was Grade 3 or louder and was accompanied by a systolic thrill. A diastolic inflow murmur at the lower left sternal border or apex was heard in all but 2 patients beyond the age of 2 months. This murmur had a low-frequency, rumbling quality and occurred in early and mid-diastole.

An evaluation of the sodium Amytal sedation test in male hypertensive patients

Veterans Administration Cooperative Study on Antihypertensive Agents

The sodium Amytal sedation test is said to have prognostic significance in that the greater the fall in blood pressure during sleep induced by sodium Amytal the better the prognosis and response to treatment. The Amytal test was described first by Allen and his associates,[1,2] who applied it as an aid in selecting patients for sympathectomy. They postulated that, in general, the greater the reduction in blood pressure during the test the better the amelioration of the hypertension after sympathectomy. Smithwick[3] used the test for the same purpose, and later[4] included it with other criteria to divide patients into prognostic categories of hypertensive cardiovascular disease. Hammarström,[5] on the other hand, found no correlation between the Amytal test response and the extent of reduction in blood pressure after sympathectomy. Schroeder[6] indicated that the blood pressure during the sodium Amytal test decreased less in nephrogenic than in essential hypertension. He also applied the test as an index of the severity of the hypertension. Werkö and Brody[7] observed diminished antihypertensive responses after sodium Amytal in patients with toxemia of pregnancy. Duncan[8] advised against the use of ganglionic blocking agents in those patients with essential hypertension whose diastolic blood pressure fell below an arbitrary level of 100 mm. Hg during the Amytal sedation test.

The present report is concerned with correlating the sodium Amytal test with the extent of cardiovascular damage and the levels of blood pressure prior to treatment, as well as with the response and mortality rate after treatment.

Methods

Details of the manner of selection of patients, classification of severity of disease, treatment, and repeated annual examinations may be found in the first report of the Veterans Administration Cooperative Study on Antihypertensive Agents.[9] The Amytal sedation test was performed during the pretreatment examination of 817 male patients with hypertension in Veterans Administration hospitals. Sodium Amytal, 0.2 Gm., was administered orally every hour for 3 hours, beginning at 7:00 P.M. The blood pressure was recorded by the ward nurse before each dose, and every hour thereafter until 7:00 A.M., that is, for 12 hours.

The information from reports of initial examination and annual re-examination was numerically coded, and punched into IBM cards by key-punch machines. A single card contained all of the pertinent,

The following Veterans Administration hospitals collaborated in this study: Birmingham; Brooklyn; Chicago, West Side; Iowa City, Oklahoma City; Richmond; San Juan, Puerto Rico, Seattle; Washington, D.C.; West Haven; and West Roxbury. The data were analyzed by Alvin D. Oscar (medical student in the Veterans Administration Summer Scholarship Program), Edward D. Freis, M.D., and John H. Williams, Jr., B.A.
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left sternal border, with the degree of splitting remaining fixed during respiration. A systolic ejection murmur along the left sternal border, and a diastolic inflow murmur at the lower left sternal border or apex are usually present. Cardiac enlargement with increased pulmonary vasculature on x-ray examination, and right ventricular hypertrophy on the electrocardiogram are constantly present.

A large pulmonary blood flow was demonstrated by catheterization and x-ray study in every case, and the atrial septal defects seen at autopsy or during operation were large. A moderately large flow gradient across the pulmonic valve was usually observed. Mild pulmonary hypertension was seen in only two instances, and in no case was there evidence of increased pulmonary vascular resistance.

Although the symptoms of cardiac failure in infants with this lesion are often transient and tend to improve with age, this present study shows that cardiac failure is not necessarily transient and benign. Early infancy is the most vulnerable period, with the symptoms occurring most commonly in the first 6 months of life and rarely after 1 year of age. This age incidence is similar to that reported by Keith and associates.[7] The severity of respiratory infection, rapid onset and progression of cardiac failure, and the promptness with which therapy is instituted are important factors in determining the course.

The frequent success of intensive treatment directed against heart failure and respiratory infections, and the feasibility of early operation in patients with atrial septal defect should allow reduction of mortality from this defect to a minimum.

Summary and conclusions

Thirteen cases of uncomplicated atrial septal defect of the secundum type are reported in which severe morbidity or death from congestive heart failure occurred in infancy. This series includes 7 autopsied cases and 6 cases in which the diagnosis was confirmed by laboratory data. The importance of early recognition of this anomaly in infants is emphasized.

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Amytal test (diagonal-lined columns in Fig. 2). The differences were small, however, and there was no correlation with the pretreatment, basal, systolic blood pressure (Fig. 1). The patients who received treatment with ganglionic blocking drugs were then analyzed separately, since they included those who had severe hypertension.[8] The results indicated that in these patients with the more severe hypertension the group with the poorest diastolic response during the sedation test exhibited higher pretreatment, basal, levels of systolic and diastolic blood pressure than did the other groups (Figs. 3 and 4).

Correlation between Amytal test responses and extent of organic complications. Grades of severity which indicated the extent of organic damage in the optic fundi, heart, kidneys, and central nervous system were arrived at as described previously.[6] There were fewer patients with Grade 4 organic changes than with the other grades of changes, but these patients with the most severe organic damage exhibited lesser falls in blood pressure during the sodium Amytal sedation test than did patients in the other groups (Table IV). For example, the 22 patients who had Grade 4 changes in the optic fundi (papilledema, hemorrhages, and/or exudates), and the 43 patients who had Grade 4 renal damage (azotemia which failed to clear after therapy for congestive heart failure) exhibited an average fall of 15.7 per cent in diastolic blood pressure during the sedation test, as compared to reductions of 19 to 21 per cent in the other groups. Patients with Grade 4 cardiac changes exhibited a fall of only 13.3 per cent in diastolic blood pressure after sodium Amytal, as compared to reductions of 19 to 21 per cent in the patients with less severe cardiac complications. Since the Grade 4 classification included only patients with congestive heart failure who were not responsive to routine therapy, it would be expected that their sleep might be disturbed even after the administration of sodium Amytal, and that, consequently, their response to the test would be poor.

Relationship between the sodium Amytal sedation test and mortality and "treatment failures." Over an average follow-up period of 2½ years there was a greater percentage of deaths and "treatment failures" in the patients who had minimal falls in diastolic pressure during the sedation test than in those who had greater responses (Table V). Death occurred in 20 per cent of the 188 patients who exhibited a fall of 0 to 9 per cent in diastolic pressure during the Amytal

Table II. Relation of history of familial hypertension to average response of blood pressure during Amytal sedation test

Number of patients and test parameters	History of familial hypertension		
	Yes	No	Unknown
Number of patients	237	169	411
Per cent fall under sedation*			
Systolic	23 1	21 5	22 1
Diastolic	21 0	19 3	20 1

*Same footnote as to Table I

Table III. Relation between duration of known hypertension and average response of blood pressure during Amytal sedation test

Number of patients and test parameters	Duration of known hypertension (yrs.)						
	0	1-5	6-10	11-15	16-20	21-30	Over 30
Number of patients	180	297	124	113	52	26	9
Per cent fall under sedation*							
Systolic	22 9	21 5	22 4	22.4	24.8	21.6	33 1
Diastolic	21 9	18 8	20 0	21 4	20.6	18.7	27 6

*Same footnote as to Table I.

Table I Relation between age and response of blood pressure during Amytal sedation test

Number of patients and test parameters	Age at time of test (yr.)				
	20-29	30-39	40-49	50-59	60-69
Number of patients	19	150	250	123	275
Per cent fall under sedation*					
Systolic	23.5	22.3	21.8	21.1	23.6
Diastolic	20.7	21.6	19.3	19.8	20.1

*Group averages of the falls in blood pressure from the presedation reading to the lowest values obtained during the Amytal sedation test

available information for one patient. The cards were grouped into four categories according to the per cent fall in the patients' blood pressure from the 7:00 P.M., or presedation, reading to the lowest values after the administration of sodium Amytal. The four grades of response, which were made separately for both systolic and diastolic pressure, were as follows: Grade 1—0 to 9 per cent reduction, indicating the poorest response; Grade 2—10 to 19 per cent reduction; Grade 3—20 to 29 per cent reduction; and Grade 4 (the best response)—30 per cent or more reduction in systolic or diastolic pressure.

The punch-card records of the 817 patients were examined for correlations between the sodium Amytal response and the following: age, race, history of familial hypertension, level of pretreatment basal blood pressure, per cent fall in blood pressure from that at time of admission to the hospital to the average blood pressure for the fourth through sixth hospital days, extent of organic damage in the optic fundi, heart, kidneys, and central nervous system, "treatment failure," and death.

Results

Per cent of patients in the various grades of response to the Amytal test. In respect to the response of the systolic blood pressure during the sedation test, 30 per cent of the patients exhibited a Grade 4 response, that is, a fall of 30 per cent or more from the presedation level; 55 per cent of the patients exhibited a reduction of 10 to 29 per cent (Grades 2 and 3), and 15 per cent exhibited a fall of less than 10 per cent. In respect to the diastolic blood pressure, approximately 20 per cent of the patients had a maximal fall of 30 per cent or more, 60 per cent had intermediate responses, and 20 per cent exhibited reductions that were less than 10 per cent of the presedation level.

Correlation between age, race, and duration and severity of hypertension and the results of the sedation test. There was no correlation between lability of systolic or diastolic blood pressure according to the sodium Amytal sedation test and age, history of familial hypertension, or duration of known hypertension (Tables I, II, and III). The average sedation test response was greater in the 9 patients who were known to have had hypertension for 30 years or longer, but their number was so small that the result lacked statistical validity (Table III). Furthermore, patients who had had hypertension for 21 to 30 years exhibited no greater responses to Amytal than did patients who had hypertension of shorter duration. There also was no correlation with race: the mean fall in blood pressure during sedation was 22.6/20.0 (systolic/diastolic) per cent in 461 Caucasians, and 22.3/19.9 per cent in 356 Negroes.

The fall in systolic blood pressure during the sodium Amytal sedation test failed to correlate in any way with the levels of pretreatment, "basal,"[8] blood pressure. In regard to the change in diastolic blood pressure during the sedation test, the patients with the poorest responses exhibited slightly higher pretreatment, basal, levels of diastolic blood pressure than did those with the greatest falls during the

patients were too small to ascribe any significance to these differences.

Since the percentage of patients who died over an average follow-up period of 2½ years was twice as great in the group which had the least fall in diastolic blood pressure as it was in the group which exhibited the greatest response to sodium Amytal, the test appeared to have some prognostic value. It was possible, however, that a similar estimate could have been made using other available criteria, particularly the severity of organic changes. If such were the case, the test would be somewhat redundant and its clinical usefulness would, therefore, be reduced considerably.

In order to examine this question, the

Table V. Relation between the response of the systolic and diastolic blood pressures to Amytal sedation and deaths and "treatment failures"

Grouping	*Per cent fall in systolic blood pressure during Amytal sedation test*				*Total*	*Per cent fall in diastolic blood pressure during Amytal sedation test*				*Total*
	0-9	*10-19*	*20-29*	*30+*		*0-9*	*10-19*	*20-29*	*30+*	
Total patients	130	204	252	231	817	188	217	229	183	817
Deaths	24	29	43	38	134	38	40	37	19	134
Per cent deaths*	18	14	17	16		20	18	16	10	
"Treatment failures"	*18*	*32*	*26*	*21*	*97*	*34*	*23*	*27*	*13*	*97*
Per cent	14	16	10	9		18	11	12	7	

*Per cent deaths over an average observation period of 2½ years.

Table VI. Time and cause of death in patients who exhibited the greatest and least response during Amytal test

Time and cause of death	*Response of diastolic blood pressure during sedation test*			
	*Least response**		*Greatest response†*	
	Number of patients	*Per cent of patients*	*Number of patients*	*Per cent of patients*
Total deaths	38		19	
Time of death from start of treatment:				
Within 6 mo.	9	24	3	16
6 mo. to 1 yr	4	11	3	16
1 yr. to 18 mo.	10	26	4	20
18 mo. to 2 yr.	8	21	2	11
More than 2 yr.	7	18	7	37
Died after leaving study	13	34	8	42
Cause of death:				
Cerebral vascular accident	3	8	3	16
Coronary artery disease	10	26	9	47
Congestive heart failure	7	18	1	5
Renal disease	5	13	3	16
Other unrelated causes	3	8	2	11
Unknown	10	26	1	[illegible]

*Fall of 0 to 9 per cent

†Fall of 30 per cent or more.

Table IV. Relation between organic damage, measured in terms of grades of severity, and the response of blood pressure during Amytal sedation test

Organ area	Number of patients and test parameters	Grades of severity* 0	1	2	3	4
Optic fundi	Number of patients	48	368	236	120	22
	Per cent fall under sedation†					
	Systolic	22.9	22.9	22.2	22.2	19.3
	Diastolic	19.6	20.3	20.2	18.7	15.7
Kidneys	Number of patients	475	174	73	45	43
	Per cent fall under sedation†					
	Systolic	22.3	21.5	22.1	20.5	18.5
	Diastolic	20.8	19.2	20.6	20.1	15.7
Heart	Number of patients	172	362	145	121	16
	Per cent fall under sedation†					
	Systolic	24.2	23.3	21.8	18.5	17.9
	Diastolic	20.9	20.6	18.6	19.0	13.3
Central nervous system	Number of patients	320	383	87	14	12
	Per cent fall under sedation†					
	Systolic	21.2	22.0	25.1	18.1	16.6
	Diastolic	20.3	19.7	22.7	13.1	15.3

*Severity graded from 0 (no abnormalities) to 4 (most severe impairment) according to criteria given in prior publication.[7]

†Group averages of the falls in blood pressure from the presedation reading to the lowest values obtained during the Amytal sedation test.

test, as compared to 10 per cent in 183 patients who showed a fall of 30 per cent or more in diastolic blood pressure. The difference was significant ($p < 0.02$). Similarly, there were 18 per cent "treatment failures" (development of severely elevated blood pressure or acute hypertensive complications) in the group with the poorest diastolic responses during the Amytal test, and only 7 per cent in those with the greatest response of diastolic blood pressure after sodium Amytal. There was no significant correlation between the percentage fall in systolic blood pressure under sedation and either death rate or "treatment failures" (Table V).

An investigation of the circumstances surrounding the deaths that occurred in the two groups of patients, those with the least and those with the greatest response to sodium Amytal, failed to reveal significant differences between the two groups. They were essentially alike in regard to the interval of treatment prior to death, age range, and cause of death. Approximately 30 per cent of the deaths in both groups occurred during the first year of observation (Table VI). Slightly more of the deaths in the group most responsive to sodium Amytal were among patients who defaulted, but this fact did not account for the difference in death rates in the two groups. The average age at death in the least responsive groups was 46, and in the most responsive it was 45 years.

In a comparison between the two groups as to the causes of death the facts were made obscure because the reason for death could not be established in 10 of the patients in the least responsive group. When these cases were excluded, it was found that there were more deaths from coronary artery disease and cerebral vascular accident, about the same percentage from renal disease, and fewer from congestive heart failure in the group with more than 30 per cent fall in diastolic blood pressure than in the least responsive group. With the exception of the fewer deaths due to congestive heart failure, the numbers of

grouping was justified by the fact that treatment was not based on response to the sedation test, and patients with varying degrees of response to the test were distributed approximately equally among the different therapeutic regimens.

After 2 years of treatment, the reduction in both the systolic and diastolic blood pressures of patients with poor responses to sodium Amytal was as great as that which occurred in those with the most marked responses during the test (Figs. 1 and 2). The patients who died or became "treatment failures" prior to 2 years, which represented the majority of such cases, would not be included in this series.

A separate analysis of those patients treated with ganglionic blocking agents disclosed a significant reduction in blood pressure after 2 years of treatment. The extent of the reduction in blood pressure, however, was not correlated with the degree of response to the sodium Amytal test (Figs. 3 and 4).

Changes in severity as related to the optic fundi, kidneys, heart, and central nervous system at the end of 2 years of treatment were also examined. The patients were divided into four groups according to the response of systolic and diastolic pressures during the Amytal sedation test. The scores reported under

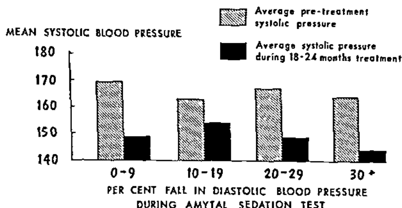


Fig. 1. Chart showing means of pretreatment (*diagonal-lined columns*) and post-treatment (*solid columns*) systolic blood pressure in 209 patients receiving various antihypertensive regimens for 2 years or longer. The patients have been divided into groups according to the degree of fall in *diastolic* blood pressure during the sodium Amytal sedation test.

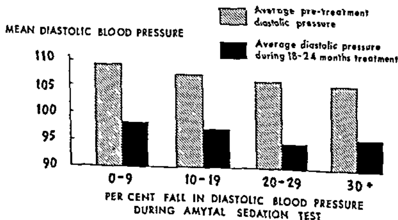


Fig. 2. Chart showing means of pretreatment and post-treatment diastolic blood pressure in 209 patients receiving various antihypertensive regimens for 2 years or longer. Other notations as in Fig. 1.

Table VII. Comparison between severity of organic changes in the optic fundi and kidneys and diastolic pressure during Amytal sedation in relation to mortality

Grades of severity*	Per cent fall in diastolic pressure during Amytal sedation test: 0-9 — Total cases	0-9 — Deaths	0-9 — Deaths (per cent)	30+ — Total cases	30+ — Deaths	30+ — Deaths (per cent)	p value
Optic fundi							
0 through 2	150	22	15	149	15	10	>0.05
3 and 4	37	16	43	30	4	13	<0.01
Renal							
0 through 2	163	26	16	165	16	10	Borderline at 0.05
3 and 4	23	12	52	14	3	22	

*See first footnote to Table IV

deaths were classified into two groups according to the extent of damage in the optic fundi and kidneys: those patients with the least and those patients with the greatest response of diastolic blood pressure after sodium Amytal. Renal impairment and changes in the optic fundi were chosen as the pertinent indices because they are considered generally to have the greatest prognostic significance. If the increased death rate among poor responders to Amytal was only a reflection of the fact that this group contained more patients with the most severe organic changes, then there should be no essential difference in *percentage* deaths *among* patients with the most severe damage in the optic fundi and kidneys regardless of their response to Amytal sedation.

The results indicated that with the same degree of impairment in the optic fundi or kidneys the per cent of deaths was higher in the group with *the least reduction in* diastolic blood pressure during the sedation test (Table VII). For example, in patients who exhibited Grades 3 (hemorrhages and/or exudates) and 4 (papilledema) changes in the optic fundi, 43 per cent of those in the group with the poorest response to Amytal died, as compared to 13 per cent in the group with the greatest falls in diastolic pressure during the test ($p < 0.01$). Similarly, in the patients with Grades 3 and 4 renal changes, there were 52 per cent deaths among the poor responders and 22 per cent among the best responders to Amytal ($p = 0.05$). Grade 3 renal complications included proteinuria of 1+ or more, urine specific gravity of 1.015 or less, and PSP excretion of 35 per cent or less in a 2-hour pooled specimen. Grade 4 severity included all cases of azotemia which failed to clear after the patient had been treated for congestive heart failure. Similar trends were seen in the patients with less damage in the optic fundi and kidneys, but the differences between good and poor responders to Amytal were of no, or only borderline, significance.

Relationship between the response of blood pressure to the sedation test and improvement of blood pressure or of organic changes during treatment. Data derived from repeated annual examinations were available in 209 patients who were followed for a period of 2 years after the beginning of treatment. Each of these patients had been administered one or another of the following regimens: placebo, reserpine alone or in combination with hydralazine, or reserpine plus one of the following ganglionic blocking drugs—pentolinium tartrate, mecamylamine, or chlorisondamine.[5] All regimens were grouped together to give a larger sample for analysis. This

Amytal. The present series was composed entirely of male hypertensive patients. If the sample is indeed representative of the male hypertensive population, the results indicate that a male patient with a fall of less than 10 per cent in diastolic blood pressure after sodium Amytal has twice the probability of dying within 2 to 3 years as has the male patient who exhibits a fall in diastolic blood pressure of 30 per cent or more. As indicated in Table V, the patients with intermediate responses of diastolic pressure during the sedation test also exhibited correlative, that is, intermediate, mortality rates. The incidence of so-called treatment failures, who represented survivors, but who developed such severe elevations of blood pressure or organic complications that a change in antihypertensive therapy was indicated, also was significantly higher in the patients with less than a 10 per cent fall in diastolic blood pressure during the Amytal test.

It seems improbable that the prognosis indicated by the Amytal test could have been duplicated using other available clinical criteria. Hypertensive patients with retinal hemorrhages, exudates, or papilledema, who exhibited falls of less than 10 per cent in diastolic blood pressure after sodium Amytal, had a mortality rate that was approximately threefold higher than that of patients who had similar funduscopic changes, but whose diastolic pressures fell more than 30 per cent during the test. A similar trend was found in the patients who had advanced renal impairment. The Amytal sedation test, therefore, appears to supplement rather than duplicate other prognostic criteria. These results also suggest that, if the patient who has advanced organic changes still exhibits a labile diastolic blood pressure as indicated by the sedation test, his disease is not so severe as that of the patient who has a "fixed" diastolic pressure. Although similar trends were found in the patients with less severe organic damage, they were not so marked, which indicates that the test has less prognostic value in milder cases of hypertension.

Although the sodium Amytal sedation test correlated fairly well with the incidence of death and "treatment failures," it was of no value in predicting therapeutic responsiveness in the surviving patients who remained in the study. The lack of correlation also held in the patients treated with ganglionic blocking agents. These results, therefore, supplied no basis for using this test as a means of selecting patients for treatment with ganglionic blocking drugs.

Summary and conclusions

Sodium Amytal sedation tests were carried out in 817 male hypertensive patients. The results are listed below.

1. There was no correlation between the response to the Amytal test and age, race, or duration and severity of the hypertension.

2. In patients with severe hypertension a fall of less than 10 per cent in diastolic blood pressure during the sedation test was associated with higher pretreatment, basal, levels of blood pressure than those in patients with severe hypertension who showed greater responses.

3. Patients with the most advanced organic complications in the optic fundi, kidneys, heart, and central nervous system exhibited a poorer average response to the sodium Amytal test than did the other patients.

4. During the follow-up period there were twice as many deaths and "treatment failures" in the patients who showed the poorest response of diastolic blood pressure to sodium Amytal as in those who showed the greatest response. Such correlation was not found with the response of systolic pressure to sodium Amytal. The combination of severe changes in the optic fundi and kidneys with a poor response to Amytal was a particularly bad prognostic indication: the percentage of deaths was approximately threefold higher in this group than in the patients with similar organic changes but a good response after sodium Amytal. The test was of insignificant prognostic value in patients with less severe organic changes.

5. In 209 patients who survived and remained in the study with unchanged treatment for at least 2 years, there was no correlation between the Amytal test results and the response to antihypertensive agents, including ganglionic blocking drugs. The fall in diastolic blood pressure

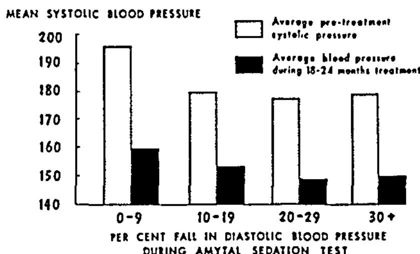


Fig. 3. Chart showing means of pretreatment and post-treatment systolic blood pressure in patients treated with ganglionic blocking agents for 2 years or longer. Other notations as in Fig. 1.

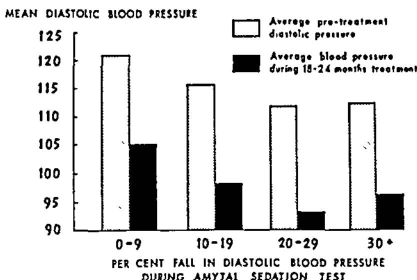


Fig. 4. Chart showing means of pretreatment and post-treatment diastolic blood pressure in patients treated with ganglionic blocking agents for 2 years or longer. Other notations as in Fig. 1.

the organ systems were arrived at by averaging the individual grades of severity.

There was no evidence in these data to indicate that the sodium Amytal sedation test was of value in predicting changes in either the optic fundi, heart, central nervous system, or kidneys after treatment. It was possible that some slight effect could have been lost because of the rather crude nature of the scoring. This analysis also excludes those who died, defaulted, or left the study for other reasons prior to 2 years of follow-up.

Discussion

The most important finding of this study was the relationship between the Amytal sedation test and the prognosis. The significant correlation with death and treatment failure was found only in the response of the diastolic, and not in that of the systolic, blood pressure to sodium

Reversal of hyperkalemic cardiotoxicity with hypertonic saline

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Hyperpotassemia constitutes a serious finding in patients with advanced renal failure since it may cause death by cardiotoxic effects which lead to the arrest of the heart in diastole. The cardiovascular alterations which occur in hyperpotassemia can be recognized with the help of the electrocardiogram, and this is of great importance in the early recognition of hyperkalemic cardiotoxic effects. In renal failure, associated electrolyte alterations might aggravate the cardiotoxic effects of excessive retention of potassium, and at a given concentration of potassium, the electrocardiographic abnormalities might be suggestive of a more advanced stage of hyperpotassemia.[1] It has also been recognized that hyponatremia apparently enhances the untoward effects of hyperpotassemia upon the heart.[1,2]

When a patient develops hyperkalemic cardiotoxicity, he is in imminent danger of death, and the removal of the potassium from the circulation is urgent in order to avoid a fatal outcome. The purpose of this communication is to report four instances in which the administration of 5 per cent hypertonic saline was successful in relieving the cardiotoxic effects of hyperkalemia and, in some instances, preserving the life of the patient.

Case reports

Case 1. A 35-year-old white, chronic alcoholic male patient was admitted for the first time to a local hospital on Feb. 4, 1960, because of swelling of the legs and abdomen, jaundice, and hepatomegaly. Because he was found to have impaired liver function, he was treated with multivitamins and bed rest for Laennec's cirrhosis. He also received a tetracycline for a pyuria that was present on repeated urine analysis. He was discharged 3 weeks after admission, markedly improved. Shortly afterward, the anorexia and jaundice reappeared and he was readmitted on March 28, 1960

Five years prior to admission the patient had had gonorrhea, which was treated with penicillin. He claimed frequency of urination, dysuria, and he recalled an episode of hematuria a few months prior to admission.

Significant findings on physical examination were pale and slightly icteric conjunctivae. A hard nodular liver was palpable 3 cm. below the xyphoid process. The left testicle was atrophic. The right testicle was edematous and tender and the cord was swollen.

The patient had a high fever in the presence of pyuria, and he was started on streptomycin and tetracycline while urine and blood cultures were made. On April 2, he developed an acute urinary retention, and, while trying to pass a catheter, it was noticed that the patient had an extremely small urethral meatus. On April 11, he had a marked hematuria. He was given blood transfusions because of a severe anemia that was evidenced by a hemoglobin value of 6.0 Gm. per cent and a volume of peaked cells of 24 mm. On April 21, the patient became unresponsive. The blood pressure was 60/0 mm. Hg, and the pulse was almost impercepti-

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rather than the fall in systolic blood pressure during the Amytal sedation test had prognostic significance and seemed to be of more value in predicting the outcome in patients with severe hypertension than in those with milder forms of hypertension.

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cision, meatotomy, and dilatation of the urethra were performed under anesthesia, without complications. The patient is alive and doing well

Case 2. A 25-year-old white woman was admitted to a local hospital with acute renal insufficiency secondary to bleeding and sepsis after an induced abortion. The patient was in oliguria for a period of 5 days, and on October 10, an electrocardiogram (Fig. 3) revealed hyperkalemic cardiotoxicity, as evidenced by bizarre QRS complexes, prolonged P-R interval, and huge upright T waves. The blood chemistries performed that day revealed a serum potassium of 8.34 mEq./L.; sodium, 100 mEq./L; chlorides, 82 mEq./L.; carbon-dioxide combining power, 11 mEq./L., and blood urea nitrogen, 103 mg per cent. The patient had a generalized flaccidity, with paresis of the lower extremities. She was given 250 c.c. of 5 per cent sodium chloride intravenously over a period of 4 hours. The paresis disappeared 20 minutes after the intravenous infusion was started. The electrocardiogram recorded the next day (Fig 3) showed marked improvement, with changes in the configuration of the QRS complexes, shortening of the P-R interval, and a decrease in the size of the T waves. Blood chemistries that day revealed that the serum potassium had decreased to 7.27 mEq./L.; the serum sodium was 110 mEq./L., carbon-dioxide combining power was 17 mEq./L., and the blood urea nitrogen was 130 mg per cent. Three days later the patient was in frank diuresis, and the serum potassium was 4.6 mEq./L. The electrocardiographic tracing obtained on October 14 was completely normal.

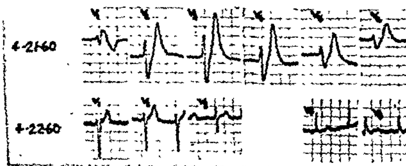


Fig. 2. The precordial electrocardiogram in Case 1. On April 21, 1960, there was hyperkalemic cardiotoxicity. A normal tracing was obtained the next morning.

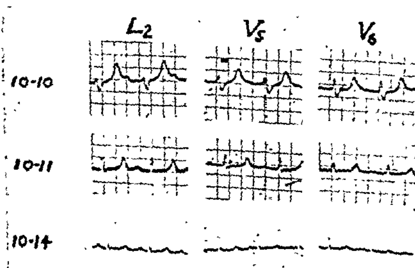


Fig. 3. Case 2. The presence of hyperkalemic cardiotoxicity is illustrated by the prolongation of the P-R interval, bizarre broad QRS complexes, and huge upright T waves on the tracing of October 10. The next day there was a marked improvement in the electrocardiogram as evidenced by shortening of the P-R interval and some reversal of the QRS and T-wave changes. Three days later (October 14) the electrocardiogram was normal.

Table I. Blood chemistries in Case 1

	April 20	*April 21**	*April 22*	*April 23*	*April 24*	*April 30*
Sodium (mEq./L.)	119.6	120	122	116	126	139
Potassium (mEq./L.)	6.98	7.8	5.2	5.6	4.5	4.7
Chloride (mEq./L.)	80	73	90	91	102	98
Carbon-dioxide combining power (mEq./L.)	6	3	——	3	5.0	17
Blood urea nitrogen (mg. %)	48	49	–	——	43.5	23

*The day of severe hyperkalemic cardiotoxicity.

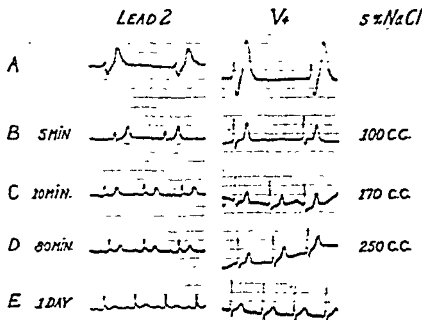


Fig. 1. Case 1. *A* illustrates severe hyperkalemic cardiotoxicity, as evidenced by bizarre broad QRS complexes, huge upright T waves, and absent P waves. In *B*, 5 minutes after the administration of 100 c.c. of 5 per cent NaCl, the heart rate has increased, there is improvement in the configuration of the QRS complexes, and the T waves have decreased in size. The presence of P waves is already noted in *C*. The electrocardiogram shown in *D* is almost normal after the patient had been given 250 c.c. of 5 per cent NaCl.

ble at less than 40 per minute. A few minutes later, both the blood pressure and pulse were imperceptible. The patient appeared to be in a terminal state, and he was gasping for breath and was unconscious. An electrocardiogram revealed changes compatible with hyperkalemia. The serum electrolyte levels from April 20 to April 30 are given in Table I.

In view of the terminal state of the patient and the electrocardiographic evidence of hyperkalemia in the presence of hyponatremia and acidosis, 5 per cent NaCl was rapidly administered intravenously as a lifesaving procedure in an attempt to reduce the effect of the hyperkalemia upon the heart. The patient regained consciousness quickly. The improvement in the cardiac condition is illustrated by the serial electrocardiograms taken while the hypertonic saline solution was being given (Figs. 1 and 2).

A cystoscopy on May 21, revealed a urethral stricture and chronic inflammation of the urinary bladder, which confirmed an obstructive uropathy as the cause of the renal insufficiency.

Bacteriologic studies cultured *Pseudomonas aeruginosa*, sensitive to kanamycin, from the urine, blood, and pus obtained from an abscess in the chest wall, thus establishing a diagnosis of Pseudomonas pyelonephritis with overwhelming sepsis. Kanamycin was given, with a gradual but definite improvement in the clinical picture, hemoglobin level, and electrolyte balance. The patient was discharged in August, 1960. In October, a circum-

septic abortion. The patient was oliguric for 7 days, but she developed a diuretic phase on May 25, 1960. On May 27, the patient had a serum potassium of 7.8 mEq./L. The serum sodium was 126 mEq./L.; chlorides, 89 mEq./L.; carbon-dioxide combining power, 14 mEq./L.; and blood urea nitrogen, 59 mg. per cent. The electrocardiogram of May 27 is illustrated in Fig. 5. The initial tracing (*A*) showed QRS complexes with some bizarre configuration and huge symmetrical peaked T waves. In an attempt to see whether these changes could be reversed with the rapid administration of sodium, this patient was given 5 per cent hypertonic saline intravenously. As illustrated in *B*, 6 minutes after the administration of 110 c.c. of 5 per cent saline, there were some significant changes in the configuration of the QRS complexes, and the T waves had decreased in size. After 210 c.c. of 5 per cent hypertonic saline, 3 hours after the original tracing, the QRS configuration in Leads I, III, V_1, and V_4 had returned to normal, and the T waves in Lead V_4 had decreased in size. A determination of serum electrolytes the next morning revealed a potassium level of 5.7 mEq./L. and a sodium level of 128 mEq./L. The diuretic phase continued, and the blood chemistries revealed a gradual return of the electrolytes to a normal level. The patient is alive and doing well.

Discussion

We have presented four instances in which the electrocardiographic alterations associated with potassium intoxication were reversed by the administration of hypertonic saline. Similar changes have been reported with the administration of sodium bicarbonate and sodium lactate.[3,7] The electrocardiographic findings in some of our patients had a poor correlation with the changes usually encountered in the plasma levels of potassium of these patients. This probably represents the influence of alterations in other ions, such as calcium and sodium, pH shifts, and altered cellular metabolism, which occur in the presence of renal insufficiency. It has been demonstrated in the experimental animal, as well as by clinical observations, that the electrocardiographic alterations associated with potassium intoxication are aggravated by the presence of acidosis, hyponatremia, and hypocalcemia.[1,3,10]

The presence of hyperkalemia with electrocardiographic alterations constitutes such a risk for the patient that this condition should be managed as a medical emergency. The removal of the excess of potassium from the body may be accomplished by hemodialysis, peritoneal lavage, use of cation-exchange resins, gastric suction, and repeated enemas. The actual removal of an adequate amount of potassium from the body might take a few hours or days, and in some instances this delay might constitute the difference between the survival and the death of the patient. In a selected group of patients the rapid control of the hyperkalemia while the removal of potassium is accomplished constitutes a lifesaving measure. A transfer of potassium from the intravascular to the intracellular space has been attempted with the use of intravenous infusions of hypertonic glucose, the use of insulin, and with the administration of anabolic hormones. When hyponatremia occurs in association with hyperkalemic cardiotoxicity, the rapid administration of sodium might overcome the cardiotoxic effects of potassium, and the removal of this ion is performed later. The administration of sodium in these patients actually lowers the level of plasma potassium, as illustrated by some of our patients in whom there was a reversal of the electrocardiographic changes as well as a drop in the serum potassium in spite of a marked oliguria or anuria. We assume, as have other investigators,[3,5] that this has been accomplished, at least in a large measure, by the intracellular transfer of potassium, although some expansion of the extracellular volume might have been a small contributing factor. Whether the reversal of the electrocardiogram is to be attributed mainly to alterations in plasma sodium has not been completely elucidated since we know that the administration of sodium is helpful in correcting the deficit of extracellular alkali which occurs in the acidosis of renal failure, and it is known that the correction of acidosis is accompanied by a shift of potassium into the cell.

It has been recognized that the cardiotoxic effects of hyperkalemia in the presence of hyponatremia may be corrected by the intravenous administration of molar sodium lactate or 5 per cent sodium bicarbonate. We have found that similar significant changes may be obtained with the use of 5 per cent sodium chloride.

Summary

Four cases of hyperkalemic cardiotoxicity are reported in which the dan-

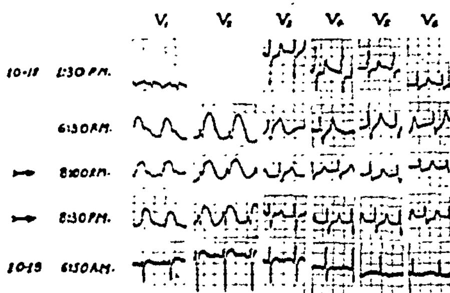


Fig. 4. Serial precordial electrocardiograms obtained in Case 3. On October 18, at 1:30 P.M., there was evidence of hyperkalemia, as manifested by QRS and T-wave changes. The cardiotoxicity increased by 6:30 P.M., as shown by QRS changes, huge upright T waves, and prolonged P-R interval. Administration of 200 c.c. of 5 per cent NaCl brought *some shortening of the P-R interval and an increase of the QRS complexes by 8:30 P.M. In spite of anuria the evidence of hyperkalemic cardiotoxicity disappeared within 10* hours and 20 minutes, and the plasma potassium decreased to 5.2 mEq./L., as shown by the lowermost tracing.

Case 3. A 29-year-old white woman received a fourth injection of Fuadin on Oct. 16, 1961, and this was followed by a severe hemolytic crises on the basis of an acquired autoimmune hemolytic process. On October 18, the patient developed oliguria, and an electrocardiogram taken at 1:30 P.M. revealed evidence of hyperkalemia, as manifested by QRS changes and tall peaked T waves in the precordial leads. Blood chemistries revealed a serum potassium of 7.05 mEq./L., serum sodium, 124 mEq./L.; chlorides, 87 mEq./L.; carbon-dioxide combining power, 21 mEq./L., and blood urea nitrogen, 54 mg. per cent. An electrocardiogram taken the same *afternoon, at 6:30 P.M., revealed severe hyperkalemic* cardiotoxicity, as evidenced by progressive QRS changes, huge upright T waves, and prolongation of the P-R interval. It was thought that the marked hemolysis was responsible for the rapid increase in serum potassium. The electrocardiograms taken at 8:00 and 8:30 P.M., after 100 and 200 c.c. of 5 per cent sodium chloride, respectively, had been given intravenously, showed only minimal improvement, as manifested by some shortening of the P-R interval, increase in the intensity of the R waves, and decrease of the T waves. Because of the severe and progressive hyperkalemic cardiotoxicity and anuria, this patient was transferred by airplane from San Juan to the New York Hospital, in New York City, for renal dialysis. The electrocardiogram taken the next morning at 6:50 A.M. at the New York Hospital prior to dialysis revealed disappearance of the hyperkalemic cardiotoxicity. The serum level of potassium that morning had dropped to 5.2 mEq./L., and the carbon-dioxide combining power was 24 mEq./L. Serial precordial electrocardiograms are illustrated in Fig. 4. She never recovered from the renal failure and died on Oct. 22, 1961.

Case 4. A 27-year-old white woman was admitted to a local hospital with acute renal failure secondary to overwhelming sepsis, which was secondary to a

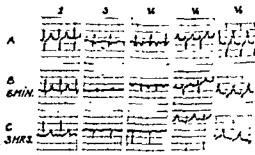


Fig. 5. Case 4. Hyperkalemic cardiotoxicity is illustrated in *A* by huge T waves and changes in the configuration of the QRS complexes. *B* and *C* illustrate the electrocardiographic changes obtained 6 minutes and 3 hours after the administration of 110 c.c. and 210 c.c. of hypertonic saline, respectively. The electrocardiogram in *C* is almost normal.

Experimental and laboratory reports

A short method for measurement of cardiac output by indicator dilution

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Among the advantages of a pooled sample technique for calibrating indicator-dilution curves is the possibility of calculating cardiac output without the need for replotting the curve and measuring its area. The principle is as follows:

Calculation of flow by indicator dilution is based on the general formula

$$F = \frac{60\ I}{\int_0^\infty C_B dt} \qquad (1)$$

where F = flow in L. per minute, I = amount of indicator injected, expressed in convenient mass units, C_B = concentration expressed in mass units per liter of blood, t = time in seconds, and the denominator of the right-hand term is the area under the curve of initial circulation.

In practice, when the dilution curve is directly recorded as a continuous function, the area is usually obtained by summing the deflections, measured in millimeters at 1-second intervals, of the semilogarithmically replotted curve of initial circulation. The area under the exponential decay limb may be extrapolated mathematically to infinity, or summation may be terminated when the falling concentration has reached an arbitrary level of absolute concentration or a given per cent of peak concentration. The resultant area (ΣD) is in *millimeter seconds* and is converted into *concentration seconds* by a calibration factor (f) which has the dimensions *concentration/millimeter*. The working formula then becomes

$$F = \frac{60\ I}{f \Sigma D} \qquad (2)$$

With an integrated sample technique,[1,2] the volume of blood traversing the densitometer over a known time interval, t_2-t_1, is collected, and the indicator concentration (C_{IS}) in that sample is related to the mean deflection of the dilution curve during that interval. Thus,

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gerous effects of the increased levels of serum potassium were relieved by the administration of hypertonic (5 per cent) saline. A rapid intravenous administration of hypertonic saline might be a lifesaving procedure in selected cases of hyperkalemic cardiotoxicity. The possible mechanisms involved were discussed.

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confined to the mitral valve, 6 with significant lesions confined to the aortic valve, and 7 with lesions at two or more valves. Severe aortic insufficiency was present in 6 patients, mild or moderate aortic insufficiency in another 6, and moderate mitral insufficiency in 3 patients.

Evans blue dye (5 mg.) or indocyanine green dye (10 mg.) was injected rapidly from a calibrated pipette,[3] with a flush of 10 ml. of saline, into the left atrium, pulmonary artery, right atrium, or superior vena cava. A syringe* drew blood at a constant rate of 0.7 ml. per second from the brachial artery, aorta, or pulmonary artery, through a cuvette densitometer,[4] the output of which was recorded photographically.† Collections from the brachial artery were through 17-gauge, thin-walled Cournand needles connected to the densitometer by 10 cm. of polyethylene tubing (I.D. 1.13 mm.). Collections from the aorta and pulmonary artery were through catheters of various sizes connected directly to the densitometer.

The ingress portal into the cuvette of the densitometer was modified to include a three-way stopcock which permitted the entrance of either blood or air into the cuvette. Curves were recorded as follows. A wedge with an optical density approximating that of blood was introduced into the densitometer light path. The withdrawal syringe was started and, immediately thereafter, the stopcock was turned to permit blood to enter the cuvette. Upon arrival of blood in the light path, the combined densities of blood and wedge produced a sharp deflection which signaled the beginning of the integrated sample collection. The wedge was then removed from the light path, the output signal adjusted to base line, the indicator injected, and the curve recorded. Inscription and the collection of blood were terminated by returning the cuvette stopcock to its original position, which resulted in immediate exclusion of blood and admission of air. The departure of blood from the cuvette produced a sharp deflection which signaled the end of the integrated sample. A representative record is shown in Fig. 2.

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The curves were monitored oscilloscopically, and sampling was terminated in one of three discrete time ranges: at the nadir of the descending limb, when the trace on the oscilloscope appeared to be parallel to the base line (Group A, Fig. 3); several seconds after the nadir, when the trace was clearly on the rising limb of the curve of recirculation (Group B, Fig. 1); or before the nadir, when exponential decay appeared to have been established, but concentration was still falling, although at a decelerating rate (Group C, Fig. 4). Review of the photographic records established that selective termination of sampling had been accomplished by visual monitoring. In all experiments of Group C, the terminal deflection was lower than the deflection 1 second earlier by several per cent of peak deflection. In all experiments of Group B, inscription had been terminated 2 or more seconds after the nadir of the curve, and the terminal deflection exceeded the nadir by several per cent of peak deflection. In Group A the final segment was flat in 36 curves, the terminal deflection being identical with the deflection 1 second earlier. In 11 curves the final segment was rising but the terminal deflection followed the nadir by < 2 seconds and exceeded it by < 1 per cent of peak deflection. In 4 curves the final segment still revealed decay, but the

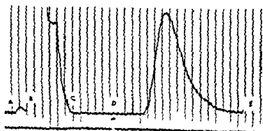


Fig. 2. Photograph of a dye-dilution record. The withdrawal syringe was started at *A*, and the stopcock was turned immediately thereafter. The sudden disappearance of the trace at *B* signaled the arrival of blood in the cuvette light path. The optical wedge was removed from the light path, the trace adjusted to base line (*C*), and the dye injected (*D*). Termination of sampling is indicated by the sudden disappearance of the trace at *E*. The interval from *B* to *E*, which is the duration of collection, is the only datum needed from the curve record to calculate cardiac output by the short method.

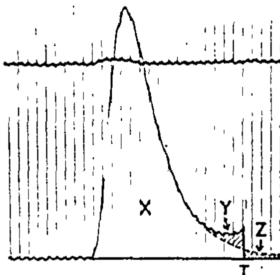


Fig. 1. Photograph of a dye-dilution curve recorded from the ascending aorta after injection of indocyanine green dye into the main pulmonary artery. Paper speed was 5 mm. per second, and time lines are at 1-second intervals. The segment of exponential decay is drawn in as a dashed line extending to 1 per cent of peak deflection. Y and Z refer to the cross-hatched and stippled areas, respectively. The area ($\Sigma D'$) under the continuously recorded curve = X + Y. The area (ΣD) under the extrapolated curve of initial circulation = X + Z. If inscription is terminated at a critical time, T_c, when Y = Z, then $\Sigma D = \Sigma D'$ and flow calculated by the short method of formula 5 will equal flow calculated by the conventional method of formula 4. If inscription is terminated at $T < T_c$, Z exceeds Y, and the short calculation will result in an overestimate of the flow calculated by the conventional formula. If, as in the case here, inscription is terminated at $T > T_c$, Y exceeds Z, and flow is slightly underestimated by formula 5. In the case illustrated the short method resulted in a 1.5 per cent underestimate. If inscription had been terminated 1 second earlier (when it was already evident that the nadir of the curve had been reached), the two calculations would have agreed within < 0.3 per cent.

$$I = \frac{C_{IS}}{(\Sigma D')/(t_2 - t_1)} \qquad (3)$$

where $\Sigma D'$ is the sum of deflections at 1-second intervals between t_1 and t_2. When concentration is measured in plasma, multiplication by the plasmatocrit (PCT) is necessary in order to convert plasma concentration to concentration in blood.

Combining (2) and (3) and incorporating the optional correction for measurement of concentration in plasma, the formula is

$$F = \frac{(60\ I)\ (\Sigma D')}{(PCT)\ (t_2 - t_1)\ (C_{IS})\ (\Sigma D)} \qquad (4)$$

With a partial integrated sample, e.g., one obtained at the "tail" of the curve[4] or during the downstroke,[3] $\Sigma D'$ will necessarily be less than ΣD. However, with a total integrated sample, consisting of the entire volume of blood collected during inscription of the curve, $\Sigma D'$ may be less than, equal to, or greater than ΣD. If inscription of the curve is terminated at a time when exponential decay has been established but recirculation is not yet evident, $\Sigma D'$ will be less than ΣD. If inscription is permitted to continue to a time beyond the peak of recirculation, $\Sigma D'$ will exceed ΣD. Somewhere between these times lies a critical time at which the two areas are equal. If inscription is terminated at this point, replotting and calculation of curve areas are unnecessary, and flow can be calculated from two spectrophotometric readings, a determination of PCT, and measurement of the duration of collection (T), by the simple formula

$$F = \frac{60\ I}{(PCT)\ (T)\ (C_{IS})} \qquad (5)$$

The situation is illustrated geometrically in the graph and legend of Fig. 1.

Since the most laborious and time-consuming step in calculating cardiac output from indicator-dilution studies consists of replotting the curve and summing deflections, there is a profound advantage in a method which makes this step unnecessary. The present study was undertaken to evaluate the usefulness of this short method for calculating cardiac output.

Methods

Sixty-six dilution curves were recorded in 28 subjects undergoing cardiac catheterization. Except for patients with left-to-right shunts or severe mitral regurgitation, who were excluded because the deformed curves pose special problems, the subjects were consecutive and unselected. Three subjects were clinically and hemodynamically normal. There were 22 patients with rheumatic heart disease, and one patient each with congenital aortic stenosis, coarctation of the aorta, and decompensated hypertensive heart disease. Among the patients with rheumatic heart disease there were 9 with significant lesions

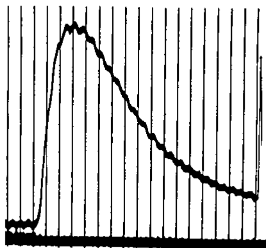


Fig. *4.* Photograph of a dye-dilution curve which was terminated when concentration was still falling, although at a decelerating rate.

discrepancy is not significantly different ($0.6 < p < 0.7$) from a discrepancy of zero, but differs significantly ($p < 5 \times 10^{-5}$) from the mean discrepancy observed in Group B or Group C.

There was no significant difference in discrepancy between curves obtained at rest and those obtained during exercise. However, as might be expected, the volume of the pathway between injection and collection sites did influence the accuracy of approximation by the short method (Table II). With short pathways, from right atrium or superior vena cava to pulmonary artery, or from left atrium or pulmonary artery to aorta or brachial artery, the mean discrepancies were equal to or close to zero. With the longer pathway, from right atrium or superior vena cava to aorta, discrepancies slightly exceeded 1 per cent, and with the longest pathway, superior vena cava or right atrium to brachial artery, the mean discrepancy was 3.1 per cent. If the cases with the longest pathway are excluded, there are no significant differences between injection sites, between collection sites, or between combinations of injection and collection sites.

Discussion

The results of this study demonstrate that cardiac output can be estimated by a short method which obviates the need for measurement, replotting, and graphic integration of continuously recorded indicator-dilution curves. The statistically insignificant disparity between these estimates and flows calculated by the conventional method is negligible for clinical purposes, lies within the error limits of dilution studies, and may be acceptable in some investigative situations.

The method is applicable in all normal subjects and in almost all varieties of congenital and acquired cardiovascular disease. The only exception among the congenital lesions is in cases of left-to-right shunts which characteristically exhibit an interruption of the decay limb of the curve. With right-to-left shunts, the method is applicable provided that injection is made distal to the shunt. The only exceptions among cases of acquired lesions are those situations in which prolongation of the downslope is so extreme as to preclude recognition of the optimal time for termination of inscription. This includes marked reduction in cardiac output, marked enlargement of central volume, and severe mitral regurgitation. With tricuspid regurgitation, the restriction can be obviated by injection into or distal to the pulmonary artery. Severe aortic insufficiency, exemplified by 6 patients in this study, does not produce a curve deformity

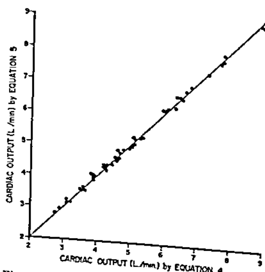


Fig. *5.* Scattergram, from the data of Group A, showing the excellent correlation ($r = 0.999$) be- tween cardiac output calculated by the conventional method (*equation 4*) on the horizontal axis and output calculated by the short method (*equation 5*) on the vertical axis.

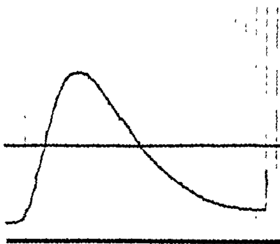


Fig. 3. Photograph of a dye-dilution curve which was terminated when the oscilloscopic trace appeared to be at the nadir of the descending limb and parallel to the base line.

terminal deflection was lower than the deflection 1 second earlier by < 1 per cent of the peak.

There were 8 studies in Group B and 7 in Group C. The largest number of experiments (51) was performed in Group A, since preliminary analysis of the data suggested that the critical time was at or near the nadir of the descending limb. In order to extend the range of flows and disappearance rates at which observations were made, 8 studies in Group A, 3 in Group B, and 1 in Group C were performed during exercise sufficient to produce a 75 per cent mean increase in oxygen consumption, a 40 per cent mean increase in output, and a rise in maximum observed flow from 7.8 to 12.2 L. per minute.

All dilution curves were plotted semilogarithmically and extrapolated to 1 per cent of peak concentration. Plasma concentrations of dye in the integrated samples were determined in a spectrophotometer (Beckman model DU) at a wave length of 625 mμ for Evans blue dye or of 805 mμ for indocyanine green dye. Plasmatocrits were determined in duplicate by centrifuging aliquots of the integrated sample in Wintrobe tubes for 30 minutes at 2,500 r.p.m. Flow was calculated by the conventional Hamilton method, using formula 4, and by the short method, using formula 5. Discrepancies between the two calculations of flow, within and between experimental groups, were evaluated by standard statistical techniques for small samples.[5] The extent to which the two calculations were related was measured using the product-moment correlation coefficient r.

Results

The results of this study are presented in Tables I and II and in Fig. 5.

When the collection of blood was terminated prior to the nadir of the curve (Group C), calculation of cardiac output by the short method resulted in a small but systematic and statistically significant overestimate. Calculated flow by the short method was an overestimate in all cases of this group. The maximum discrepancy between flows calculated by the two methods was +7.8 per cent, and the median discrepancy was +4.1 per cent. The mean discrepancy was +0.158 L. per minute or +4.0 per cent and differs significantly ($p < 0.005$) from a discrepancy of zero.

When the collection of blood was terminated 2 or more seconds after the nadir of the curve (Group B), calculation of cardiac output by the short method resulted in a small but systematic and statistically significant underestimate. Seven of the 8 cases were underestimates. The maximum discrepancy was −5.9 per cent and the median discrepancy was between −3.4 and −2.9 per cent. The mean discrepancy was −0.299 L. per minute or −2.9 per cent and differs significantly ($p < 0.01$) from a discrepancy of zero.

When sampling was terminated at the apparent nadir of the curve, there was a very small, random, and statistically insignificant discrepancy, and an excellent ($r = 0.999$) correlation (Fig. 5) between the two estimates of flow. There were 25 overestimates, 25 underestimates, and 1 instance of identical estimates. In 51 per cent of the cases the two estimates agreed within ±1 per cent, and in 94 per cent of the cases, within ±2 per cent. The largest discrepancy was a 4.4 per cent overestimate. The mean and median absolute discrepancies (i.e., without regard to sign) were ±1 per cent. With sign taken into account, the median discrepancy was zero, and the mean discrepancy was +0.005 L. per minute or +0.2 per cent. This mean

Table I. Comparison of cardiac outputs calculated by the conventional formula and by the short-cut method—Cont'd

C.O.* (L./min.)	C.O.s* (L./min.)	Discrepancy: C.Os.-C.O. (L./min.)	% Discrepancy: $\frac{C.O_s.-C.O.}{C.O.} \times 100\%$	Injection site†	Collection site†	Patient status‡
			Group B			
4 251	4 106	−0 145	−3 4	PA	AO	R
12 217	11 501	−0.716	−5 9	PA	AO	E
3 410	3 376	−0.034	−1 0	RA	AO	R
5 638	5 473	−0 165	−2 9	PA	AO	R
5 565	5 320	−0 245	−4 4	PA	AO	E
9 364	8 864	−0 500	−5 3	PA	AO	E
4.120	4 046	−0 074	−1 8	PA	AO	R
3 222	3 268	+0 046	+1 4	RA	BA	R
			Group C			
8 888	9 207	+0 319	+3 6	PA	AO	E
5 139	5 169	−0.030	+0 6	LA	BA	R
4 294	4 481	+0 187	+4 4	PA	BA	R
4 108	4 275	+0 167	+4 1	LA	BA	R
2 443	2 634	+0 191	+7.8	LA	AO	R
2 749	2.939	+0 190	+6 9	LA	BA	R
4 160	4 183	+0 023	+0 6	PA	AO	R

*C O Flow by conventional method C O s Flow by short method
†SVC: Superior vena cava, RA. Right atrium, PA. Pulmonary artery, LA. Left atrium, AO. Aorta. BA. Brachial artery.
‡R. Rest. E Exercise.

Table II. The influence of injection site and collection site on mean per cent discrepancy between cardiac outputs calculated by the conventional formula and those calculated by the short method

Injection site*	Collection site* PA	AO	BA	Total
LA	—	0 (4)†	−0 2 (6)	−0 1 (10)
PA	—	0 (31)	−0 5 (2)	0 (33)
RA or SVC	−0 2 (2)	+1 1 (3)	+3 1 (3)	+1.5 (8)
Total	−0 2 (2)	+0 1 (38)	+0 7 (11)	+0 2 (51)

*Abbreviations for sites as in Table I
†Numbers in parentheses = number of experiments on which each mean per cent discrepancy is based.

Table I. Comparison of cardiac outputs calculated by the conventional formula and by the short-cut method

CO* (L./min.)	CO_s* (L./min.)	Discrepancy, CO_s–CO (L./min.)	% Discrepancy: $\frac{CO_s - CO}{CO} \times 100\%$	Injection site†	Collection site†	Patient status‡
			Group A			
4.601	4.551	−0.051	−1.1	PA	BA	R
5.037	4.965	−0.072	−1.4	LA	BA	R
4.216	4.288	+0.072	+1.7	PA	AO	R
6.013	6.008	−0.005	−0.1	PA	AO	R
6.514	6.500	−0.014	−0.2	PA	AO	E
6.101	6.103	+0.002	0.0	PA	AO	R
6.685	6.704	+0.019	+0.3	PA	AO	R
5.306	5.233	−0.073	−1.4	LA	AO	R
4.972	4.904	−0.068	−1.4	PA	AO	E
7.748	7.719	−0.029	−0.4	PA	AO	E
6.810	6.871	+0.061	+0.9	RA	AO	R
7.807	7.890	+0.083	+1.1	SVC	AO	R
3.595	3.584	−0.011	−0.3	LA	AO	R
3.499	3.567	+0.068	+1.9	PA	BA	R
4.569	4.565	−0.004	−0.1	PA	AO	R
4.653	4.587	−0.066	−1.4	PA	AO	E
4.797	4.810	+0.013	+0.3	PA	AO	E
2.901	2.927	+0.026	+0.8	PA	AO	R
3.195	3.173	−0.022	−0.7	PA	AO	E
4.690	4.720	+0.030	+0.6	PA	AO	R
4.608	4.810	+0.202	+4.4	PA	AO	R
8.863	8.857	−0.006	−0.1	PA	AO	E
4.240	4.262	+0.022	+0.5	LA	AO	R
4.252	4.266	+0.014	+0.3	LA	BA	R
6.113	6.119	+0.006	+0.1	PA	BA	R
3.921	3.973	+0.052	+1.3	RA	AO	E
5.116	5.189	+0.073	+1.4	PA	AO	R
3.600	3.597	−0.003	−0.1	PA	AO	E
3.552	3.544	−0.008	−0.2	LA	BA	R
6.423	6.550	+0.127	+2.0	PA	AO	R
7.699	7.631	−0.068	−0.9	PA	AO	E
4.566	4.494	−0.072	−1.6	LA	BA	R
3.097	3.229	+0.132	+4.3	SVC	BA	R
5.089	5.247	+0.158	+3.1	SVC	BA	R
3.097	3.152	+0.055	+1.8	SVC	BA	R
7.314	7.295	−0.019	−0.3	SVC	PA	R
4.301	4.306	+0.005	+0.1	PA	AO	R
6.509	6.509	0.000	0.0	RA	PA	R
3.906	3.953	+0.047	+1.2	LA	AO	R
3.911	3.972	+0.061	+1.6	LA	BA	R
4.270	4.207	−0.063	−1.5	PA	AO	R
5.329	5.238	−0.091	−1.8	PA	AO	E
2.784	2.797	+0.013	+1.6	PA	AO	R
3.616	3.576	−0.040	−1.1	PA	AO	E
3.897	3.908	+0.011	+0.3	LA	BA	R
6.338	6.221	−0.117	−1.8	PA	AO	R
6.064	6.056	−0.008	−0.1	PA	AO	R
8.929	8.802	−0.127	−1.4	PA	AO	E
5.100	5.023	−0.077	−1.5	PA	AO	R
3.944	3.962	+0.018	+0.5	PA	AO	R
4.427	4.393	−0.034	−0.8	PA	AO	R

This *method* results in an appreciable saving of time by obviating the need for measurement, replotting, extrapolation, and summation of the deflections of a continuously recorded dilution curve.

Addendum

Since the preparation of this manuscript, the short method has been applied to an additional 51 dilution curves, with the same results. The mean discrepancy in the additional observations was 0.2 per cent of cardiac output, and the maximum discrepancy was a 3.6 per cent overestimate.

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comparable to that seen in mitral insufficiency, and the short estimate can, therefore, be used. It is evident that the limiting factor is not the anatomic lesion but the concomitant deformity of the dilution curve. Inapplicability of the method in any given instance results from gross abnormality of contour and will be obvious.

The advantages in simplicity and the saving of time are evident. In these respects, the present method is comparable to other attempts at simplified calculation, such as the forward triangle method[7,8] and the "emergency" formula of Dow.[9] A corollary advantage is the availability of flow estimates while physiologic studies are in progress. An additional advantage is in the possibility of salvaging those "problem" curves* in which the contours of the recorded curve are entirely normal, but in which the crown of the curve is above the recorder scale. In such an instance, one may either estimate flow by the short method or, if a more complete statement is desired, establish the limits of output for the study.

If, for example, in such a case, I = 5 mg., C_{18} = 2.5 mg. per liter, PCT = 0.60, T = 40 seconds, $\Sigma D'$ (the sum of the recorded deflections) = 530, and ΣD (the sum of the extrapolated semilogarithmic replot of the recorded deflections) = 500, one may say that

$$\frac{(60)\,(5)}{(2.5)\,(0.6)\,(40)} < \text{flow} < \frac{(60)\,(5)\,(530)}{(2.5)\,(0.6)\,(40)\,(500)},$$

or that, if an estimate of cardiac output could be made by the conventional Stewart-Hamilton method, it would lie between 5.0 and 5.3 L. per minute.

It will be evident that an estimate of flow is possible by the short method without any measurements from the curve record at all, since the duration of collection, which is the only datum required from the record, can be measured by stopwatch during monitoring or can be calculated by dividing the volume of blood collected by the sampling rate. However, the curve must be carefully inspected. In addition to oscilloscopic or other monitoring during inscription, the curve record should be reviewed to ensure that the termination was, indeed, accomplished at the desired time, and that curve contours are normal.

The essential condition, selective termination of collection at or near the nadir of the curve, has been found to be easily accomplished by means of visual monitoring. There is, of course, no reason why inscription cannot be terminated automatically by a servomechanism. In this connection, the special mathematical properties of a minimum (e.g., the first derivative of the curve = zero at its nadir) can provide particularly convenient and simple signals with which to initiate automatic termination of collection.

Summary

This report describes a short method for measuring cardiac output by indicator dilution. The premise of the method is that, if inscription of a continuous curve is terminated when the area under the recorded curve equals the area under the extrapolated curve of primary circulation, calculation of flow requires knowledge only of the amount of indicator injected, the concentration of indicator in the volume of blood collected, and the duration of collection.

Sixty-six studies were performed in 28 subjects, using 7 different combinations of injection and collection sites, and with outputs ranging from 2.4 to 12.2 L. per minute. When inscription was terminated at the apparent nadir of the descending limb, or within 2 seconds thereafter, there was a statistically insignificant difference (mean difference = 5 ml. per minute or 0.2 per cent) between flows calculated by the short method and those obtained by the conventional method. Visual monitoring of the curve readily permitted termination of inscription and collection at the desired time.

*It was the salvage application of this technique, in earlier work in another laboratory,[8] which first suggested to one of us the general usefulness of the short method as a means of estimating cardiac output.

test dose of angiotensin, 1 ml. of a 5.4 per cent sodium chloride–Krebs' solution was added to the muscle chamber. To exclude hypertonicity as a determining factor, similar experiments were conducted adding 1 ml. of a 57 per cent sucrose–Krebs' solution in place of the former.

Methods

The procedures employed were as follows:

1. Each strip of smooth muscle was stretched under a tension of 4.0 grams for 2 hours.

2. To obtain a *control response*, 0.3 gamma of angiotensin* (0.1 ml. of a 3-gamma solution) was added directly to the Krebs' solution in the muscle chamber. The response was observed over a 15-minute period. The chamber was then flushed five times before fresh Krebs' solution was added, and 1 hour was allowed for relaxation.

3. *To study the effect of a 25 per cent reduction in the external sodium ion concentration:* Two control responses were obtained and 1 hour was allowed for relaxation. The chamber was then flushed five times before addition of the solution with the lowered content of sodium. Immediately, 0.3 gamma of angiotensin was added to the chamber, and the response of the strips was observed for a 15-minute period. The system was then flushed five times before fresh Krebs' solution was added, and, after suitable time for relaxation, a final control response was obtained.

4. *To study the effect of a 25 per cent increase in the external sodium ion concentration:* Two control responses were again obtained. At the peak of the second control response to the test dose of angiotensin, 0.9 mEq. of Na^+ ion in the form previously described was added directly to the Krebs' solution in the muscle chamber. The response was observed for 15 minutes. The system was then flushed five times before fresh Krebs' solution was added, and 1 hour was allowed for relaxation. A final control response was then obtained. Each strip was also tested with the osmotically equivalent sucrose–Krebs' solution in similar manner.

*In the form of Hypertensin, supplied through the courtesy of Albert J. Plummer, M.D., Research Department, Ciba Pharmaceutical Products, Inc., Summit, N. J.

5. *To determine the effect of benzydroflumethiazide on the response of the strips to 0.3 gamma of angiotensin:* Two control responses were obtained. Benzydroflumethiazide* (5 mg. dissolved in 0.5 ml. of deionized water) was then added to the Krebs' solution in the muscle chamber, and 15 minutes were allowed for equilibration. The response of the strips to a test dose of angiotensin was then observed. The system was flushed five times before fresh Krebs' solution was added, and a final control response was obtained.

Results

I. *Reproducibility of response of muscle strips to repeated similar doses of angiotensin.* Table I illustrates the reproducibility of the response of seven strips of aorta to four repeated doses of 0.3 gamma of angiotensin. Tachyphylaxis was not observed. Reproducibility was noted consistently during the second, third, and fourth responses. In strips *F* and *G* the response for the initial run was lower than subsequent ones. The reason for this was not apparent. Therefore, the per cent change as calculated was based upon the height of the responses excluding the first run. To further assure accurate reproducibility, more than two control responses were obtained for each strip tested.

II. *Effect of acutely reducing the external sodium ion concentration by 25 per cent on the responsiveness of the muscle strips to synthetic angiotensin.* The sodium concentration of the original Krebs' solution and of the solution which had a 25 per cent reduced content of sodium was analyzed by a flame photometer prior to, immediately after, and 15 minutes after introduction into the muscle chamber. The sodium concentration of all solutions remained unchanged, indicating no measurable transfer of sodium across the cell membrane during the time period studied.

Table II demonstrates the effect of a 25 per cent reduction in the external sodium ion concentration on the responsiveness of five strips of aorta to 0.3 gamma of angiotensin. It is evident that in all those tested an enhancement of the response of the strips resulted, as compared to control re-

*Supplied as Naturetin through the courtesy of Dr Bernard Widmer, Squibb Institute for Medical Research, New Brunswick, N. J.

The reactivity to angiotensin of rabbit aorta strips after either alterations of external sodium environment or direct addition of benzydroflumethiazide

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The benzothiadiazine diuretics effect a reduction in blood pressure in a significant number of hypertensive subjects treated with these drugs. They produce a naturesis, chloruresis, and an associated mild kaluresis.[1] After therapy with these agents, hypertensive subjects also demonstrate a depressed response to infused norepinephrine[2] and an exaggerated reaction to the ganglioplegic drugs.[3] Although their exact mechanism of action still remains an enigma, their antihypertensive effect seems to be linked in some manner with the metabolism and excretion of salt.

To further investigate this mechanism, a study was undertaken of the effects of alteration of the external sodium environment on the responsiveness of spiral strips of rabbit aorta to given doses of synthetic angiotensin. Observations were also made to ascertain whether benzydroflumethiazide would directly inhibit the effect of angiotensin on the strips of aorta.

Materials

Normal unanesthetized adult rabbits were sacrificed by a blow on the head and exsanguination. Spiral strips of rabbit aorta were prepared by the method described by Furchgott.[4] The apparatus employed was patterned after that used by Helmer.[5] Unless otherwise specified, the strips were bathed in Krebs' bicarbonate solution containing 0.01M glucose[6] into which 95 per cent oxygen and 5 per cent carbon dioxide were continuously bubbled. Records were made on a kymograph drum using heat-sensitive paper.

To produce a 25 per cent reduction in the external sodium ion concentration, the sodium chloride content of the Krebs' bath was lowered by 25 per cent, 71.8 mM. of sucrose being added to maintain osmolar continuity. Both the standard Krebs' bath and the above-mentioned solution were analyzed by an osmometer prior to each experiment, and were found to contain 310m osmols per liter.

To obtain a 25 per cent increase in the external sodium ion environment without altering the concentrations of K^+, Ca^{++}, or Mg^{++} in the original Krebs' solution, it was necessary to use a hypertonic solution. At the height of the response of the strips to a

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Table II

Strip	Response (Control 1)	Response (Control 2)	Response to 25% reduction in Na^+	Response (Control 3)	Per cent change of controls	Per cent change with 25% reduction in Na^+
H	48	48	52	48	0.0	+8.3
I	56	59.5	64.5	60.5	+0.8	+7.5
J	45	42.5	47	40	−3.0	+13.9
K	25.5	29	31.5	25	−7.0	+16.6
L	22.5	27	31.5	22	−10.2	+28.5

The numbers represent height of the response in millimeters of stylus deflection.

Table III

Strip	Response (Control 1)	Response (Control 2)	Response to 25% increase in Na^+	Response to sucrose	Response (Control 3)	Per cent change of controls	Per cent change with increased Na^+	Per cent change with sucrose
M	28	28	28 to 18 (10)	27 to 23 (4)	28	0.0	−35.7	−14.2
N	14	15.5	15.5 to 10.5 (5)	16 to 14 (2)	16	+3.2	−33.3	−12.7
O	26	34	34 to 17 (17)	33 to 30 (3)	33	−1.4	−41.7	−8.9
P	20	22	22 to 15 (7)	22 to 19 (3)	23	+2.2	−33.3	−15.6
Q	20	21	21 to 11 (10)	20 to 19 (1)	20	−2.4	−48.7	−2.4

The numbers represent height of the response in millimeters of stylus deflection. The numbers in parentheses represent the total fall in millimeters of the stylus.

Table IV

Strip	Response (Control 1)	Response (Control 2)	Response after addition of benzydroflumethiazide	Response (Control 3)
R	23	22	23	22
S	26	26	27	27
T	29	29	28	28
U	38	38	40	40
V	23	22	22	23

The numbers represent height in millimeters of stylus response.

after alteration of the external sodium ion environment. Also, these effects occur before any readjustment of the levels of sodium might be expected to take place, and before alterations in the electrolytic constitution of living tissue can occur.

Conceivably, other more complex and as yet unrecognized physiochemical phenomena involving sodium metabolism and its relationship to the membrane potential or to the contractile apparatus could also occur. On the other hand, shifts in other ions, i.e., K^+ or Ca^{++}, or the transfer of water may attend alterations of sodium either in vivo or in vitro, or both. Such studies are now under investigation.

The significance of this work relates to a possible mechanism of action of the benzothiadiazine diuretics. It is known that these agents induce a diuresis of sodium and water in man. In certain hypertensive subjects a significant reduction in both systolic and diastolic blood pressure results. This response of the blood pressure does not

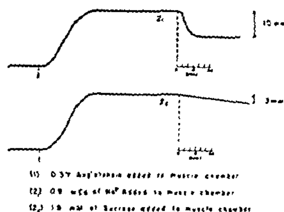


Fig. 1. See text.

sponses, when the strips were bathed in the reduced sodium environment.

III. *Effect of acutely increasing the external sodium ion concentration by 25 per cent on the responsiveness of the muscle strips to synthetic angiotensin.* Table III shows the effect of either the addition of a sodium chloride Krebs' solution or an osmotically equivalent sucrose Krebs' solution at the height of the response of the strips to 0.3 gamma of angiotensin. By comparing the per cent change of the controls to that observed after the addition of either the hypertonic salt solution or the osmotically equivalent sucrose solution, it is evident that both cause a reduction in the response. However, the salt solution produced a more prompt and significant reduction in response than did the hypertonic sucrose solution in all strips tested (see Fig. 1).

IV. *Effect of benzydroflumethiazide on the responsiveness of the muscle strips to synthetic angiotensin.* Table IV illustrates that the direct addition of benzydroflumethiazide to the Krebs' bath did not affect the response of the strips to angiotensin, as compared to control responses.

Discussion

These results demonstrate that, in vitro, an association exists between the responsiveness of the smooth muscle of the rabbit aorta to the concentration of sodium in the surrounding medium. This association may be direct, indirect, or merely a nonspecific phenomenon.

Friedman and associates[8] have suggested that acute changes in the external sodium ion concentration are attended by alterations in smooth muscle tone. They postulate that a change in the extracellular-to-intracellular sodium gradient may be the primary determinant of this altered tone. A decrease in the gradient is associated with an increase in resting smooth muscle tone and also an augmented response to certain pressor substances. Conversely, an increase in the gradient is associated with a decrease in the responsiveness of smooth muscle strips to various pressor agents. Our observations support the thesis that manipulation of the external sodium ion environment alters vascular reactivity to the pressor agent, angiotensin. This effect is most probably mediated via a change in the gradient. This is supported by the observation that in our preparation there is no measurable transfer of sodium across the cell membrane

Table I

Strip	*Response 1*	*Response 2*	*Response 3*	*Response 4*	*Per cent change*
A	22	22	21	22	−4.5
B	33	34	35	35	+1 4
C	6	6	6	6	0.0
D	23	22	22	22	0.0
E	10	9	9	9	0.0
F	30	38	38 5	39.5	−0.6
G	19	22	22	2	+2.3

The numbers represent the height of the response in millimeters of stylus deflection, as measured from the base line recorded just prior to the addition of 0.3 γ angiotensin to the peak rise of the response. The per cent change is calculated by averaging Responses 2 and 4, and then subtracting the value of Response 3 from this average. This difference is divided by the average, and the result is multiplied by 100 to yield the per cent. If Response 3 has a higher value than the average, the per cent change is positive; if a lower value is obtained, the per cent change is negative.

Pressure-volume characteristics of the diastolic left ventricle of man with heart disease

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Left ventricular end-diastolic pressure and volume are factors that play a role in regulating left ventricular output and work.[1-16] Studies by others in experimental animals indicate that an increased left ventricular end-diastolic volume for a given level of left ventricular work is one of the early signs of left ventricular failure,[1,3] and the increased volume is associated with an elevation of left ventricular filling pressure.[3,4,7] These observations are known to apply to man in whom left ventricular failure is associated with left ventricular enlargement and elevated left ventricular filling pressure, or one of the indirect measures of filling pressure, such as pulmonary "capillary" or left atrial pressure.[11-13] Because of the difficulty in determining the specific volume of the cardiac chambers, it has been common practice to define left ventricular function or failure in terms of filling pressure in both experimental animals and man.

The extent to which an increased left ventricular diastolic volume is reflected by an increased filling pressure is dependent upon the pressure-volume characteristics of the diastolic left ventricle. Studies of the normal canine left ventricular pressure-volume characteristics indicate that increases in left ventricular volume are associated with small rises in filling pressure until the left ventricular volume becomes large, after which, further increases in volume are associated with progressively larger rises in filling pressure.[2,3,6,10,14-16] Little is known about the pressure-volume characteristics of the diastolic left ventricle of normal man or the effects of disease on these relationships. This information is of importance in evaluating the meaning of ventricular filling pressure in man with chronic heart disease. This is particularly true since left ventricular filling pressure has been so widely used to assess the functional state of the left ventricle. If chronic heart disease in man is associated with changes in left ventricular pressure-volume characteristics, it will be necessary to re-examine some of the concepts of left ventricular failure in man that are based on the measurement of filling pressure. The purpose of this study is to describe the pressure-volume characteristics of the diastolic left ventricle in a group of human subjects with heart diseases of varying

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occur in a normotensive individual. The early antihypertensive effect of these agents is thought to result from a decrease in plasma volume with an associated reduction in cardiac output.[7,8] Within 1 week, however, cardiac output has returned to pretreatment levels, and within 3 to 6 months the plasma volume is only minimally reduced or has returned to normal.[9] In spite of these later changes, blood pressure remains lowered.

Friedman and associates,[10] in studies employing rats, found that these agents cause a loss of both intracellular and extracellular sodium. He suggests that this transfer of sodium is attended by a shift in water, with a resultant increase in the pre-existing sodium gradient and a decrease in smooth muscle tone. If such occurs, the reactivity to a circulating humoral substance might be decreased, as our experiments would indicate.

The possibility that the oral diuretics might effect a direct, specific antagonism of angiotensin is not supported by our observations.

Thus, it is certainly conceivable that, after treatment with oral diuretics, systemic alterations in the distribution of sodium might result in a decrease in the resting smooth muscle tone and/or a reduced responsiveness of the vascular bed to such factors as nervous stimuli or, perhaps, local or circulating humoral agents.

Summary

Studies employing spiral strips of rabbit aorta bathed in Krebs' bicarbonate media resulted in the following observations: (1) The responsiveness of single strips of rabbit aorta to repeated similar doses of angiotensin was reproducible. (2) An acute reduction of the external sodium ion concentration with a probable decrease in the Na_o/Na_i gradient enhanced the response of the strips of aorta to angiotensin. (3) An acute increase in the external sodium ion concentration with a probable increase in the Na_o/Na_i gradient lessened the response of the strips of aorta to angiotensin. (4) A benzothiadiazine derivative exerted no local specific inhibitory effect on the response of the strips of aorta to angiotensin.

These results have been discussed with respect to the mechanism of action of diuretic agents in the therapy of hypertension.

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lengths was corrected for x-ray distortion due to nonparallel x-ray beams by the following equation:

$$At = \frac{(h - b)\, Ap}{h} \qquad (3)$$

where At = true length of an object placed parallel to a given x-ray film and perpendicular to the x-ray beam, Ap = projected length, h = x-ray tube-to-film distance, and b = object-to-film distance. Tube-to-film distances were directly measured, and left-ventricle-to-film distances were calculated through recording the relationship of the left ventricle to each central x-ray beam on the films.[19] To calculate chamber volume, the two transverse chamber diameters, determined from A-P and lateral films, and the maximum measured length, whether in the A-P or lateral film, were used as the axes in the ellipsoid formula (1). Each calculated volume was corrected by applying the regression equation for this method:

$$V' = .928\,V - 3.8 \qquad (4)$$

where V′ = corrected volume in cubic centimeters, and V = volume calculated by applying equation (1). This regression equation was defined from postmortem studies on human hearts in an earlier investigation, the report on which also contains a detailed description of the method used for correcting for x-ray distortion and calculating chamber volume.[19]

Satisfactory left ventricular opacification for the purpose of calculation of volume was usually observed over 3 to 4 heartbeats. The volume calculated from each set of A-P and lateral films was plotted with respect to time after the onset of QRS of the electrocardiogram and with respect to ventricular pressure. These calculated volumes were then connected with a smooth line to form a volume curve, as illustrated in Fig. 3. This volume curve is a composite of observations on volume over a series of 3 to 4 beats.

Left ventricular pressures were recorded by a P-23G Statham strain gauge transducer and a multichannel direct-writing recorder during angiocardiography in 7 subjects (see Fig. 4), and just prior to angiocardiography in 6 subjects (see Fig. 5). Zero pressure reference was placed 10 cm. above the backs of the subjects. The left ventricle was catheterized by the transbronchial left heart catheterization technique[21] in 8 subjects; the bronchoscope and needle were removed, leaving the small

Table I

Subjects	*Diagnosis*	*Site of angio-injection*	*EDV (c.c.)*	*ESV (c.c.)*	*EDP (mm. Hg)*	*EDV/M.²* (*c.c.*)
In Fig. 4						
A	RHD with MS	RA	71	21	7 5	47
B	RHD with MS, MI	SVC	141	64	13 0	86
C*	RHD with MS, MI	LV	169	80	8 5	96
D	RHD with AS, AI	RA	213	91	13 0	107
E	RHD with AS, AI	LV	259	100	22.5	148
F*	RHD with MS, MI, AI	LV	221	144	12 0	111
G	RHD with AS, AI	LV	280	200	31.0	170
In Fig 5						
A	RHD with AS, MS	RA	113	28	15 0	63
B	RHD with MI, MS	RA	191	32	7.5	140
C	RHD with MS, AS, AI	RA	133	33	10.0	76
D	MI from ruptured chordae tendineae	RA	290	103	21.0	144
E	RHD with AI	RA	214	100	5.5	111
F	Post-SBE with AI	RA	443	234	60 0	196

*Atrial fibrillation

RHD: Rheumatic heart disease. MS: Mitral stenosis. MI: Mitral insufficiency. AS: Aortic stenosis. AI: Aortic insufficiency. SBE: Subacute bacterial endocarditis. RA: Right atrium. SVC: Superior vena cava. LV: Left ventricle. EDV: End-diastolic volume. ESV: End-systolic volume. EDP: End-diastolic pressure. EDV/M²: End-diastolic volume per square meter of body surface area.

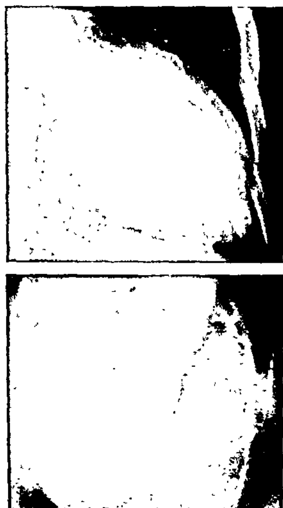


Fig. 1. Biplane angiocardiogram of the left ventricle. Anteroposterior (*top*) and left lateral (*bottom*) projections.

etiology, severity, and duration. These studies have been reported in part in preliminary form earlier.[17]

Methods

The subjects were studied while they were in the recumbent position and the postabsorptive state after premedication with meperidine, 25 to 50 mg., pentobarbital, 0.1 Gm., and scopolamine, 0.3 mg. The clinical diagnoses of these subjects are shown in Table I. Left ventricular chamber volumes were calculated from biplane angiocardiograms taken with a Schonander biplane film changer at 4 to 6 films per second in the anteroposterior (A-P) and left lateral projections (Fig. 1). X-ray exposure was 1/30 second at 300 to 400 milliamperes and 100 to 120 kilovolts. X-ray tube-to-film distances were approximately 86 cm. in the lateral projection and 100 cm. in the A-P projection. Fifty cubic centimeters of 70 per cent sodium acetrizoate* was injected under 4 to 6 kilograms of pressure through a No. 9 Lehman angiocardiographic catheter into the right atrium or pulmonary artery in 9 subjects. In 4 subjects, 40 c.c. of 75 per cent Hypaque† was injected under 6 kilograms of pressure directly into the left ventricle after retrograde aortic catheterization from the right radial artery or percutaneously from a femoral artery.[18] The time of each x-ray exposure with reference to the electrocardiogram and intracardiac or intravascular pressures was recorded by a photocell activated at the time of each x-ray exposure, as illustrated in Fig. 2.

To calculate left ventricular chamber volume from the biplane x-ray films, it was assumed that the left ventricle could be represented as an ellipsoid figure and the volume calculated from an ellipsoid formula:

$$V = \frac{4}{3} \pi \frac{l}{2} \cdot \frac{d'}{2} \cdot \frac{d''}{2} \qquad (1)$$

where l = length of the major axis of the ellipsoid, and d′ and d″ = lengths of the minor axes.

The axes were determined as follows: the margins of the opacified left ventricular chamber were traced on each film, the chamber area on each film was determined by planimetry, and the maximum chamber length on each film was directly measured. Because of difficulty in establishing and applying criteria for directly measuring the transverse chamber diameters, and because the projection of an ellipsoid is an ellipse, we calculated the transverse diameters using an ellipse formula:

$$d = \frac{4A}{\pi\, lm} \qquad (2)$$

where d = transverse chamber diameter, A = area on a given film, lm = length of the left ventricle on a given film.

Each of the diameters and measured

*Urokon, Mallinckrodt Chemical Works, New York.
†Hypaque, Winthrop Laboratories, New York.

metric relaxation characterized by a rapid fall of ventricular pressure without change in volume. Subjects with severe aortic or mitral valvular insufficiency showed little isometric relaxation (*E* of Fig. 4, and *D*, *E*, *F* of Fig. 5). The period of isometric relaxation was followed by a period when ventricular pressure continued to fall while ventricular volume began to increase. The magnitude of the change in volume during this portion of the curve was greatest in subjects with aortic insufficiency or severe mitral insufficiency. However, the shape of this portion of the pressure-volume curves was not precisely defined by this study because of limitations of the methods: (1) during this short interval of time there were relatively few observations on volume; and (2) slight damping of the ventricular pressure curve, which is often difficult to detect, will change the shape of this portion of the pressure-volume curve.

After the nadir of the ventricular pressure curve, large increases in volume were associated with small increases in pressure. In fact, the increase in filling pressure during this portion of the curve was so slight that it was barely detectable in some subjects, although changes in volume were large. Toward the end of diastole, the pressure-volume curves of subjects *B*, *D*, *F*, and *G* of Fig. 4 and subjects *A*, *C*, *D*, and *F* of Fig. 5 became considerably more steep, which indicates progressively larger increases in pressure associated with increases in volume. This was particularly evident from curves of subjects in whom postextrasystolic pauses or bradycardia provided observations over more prolonged periods of diastole. Also, the additional volume of blood delivered to the ventricle by atrial contraction occasionally made evident this break in the ventricular pressure-volume curve, which is the case in Fig. 3.

In spite of the qualitative similarities in the shapes of the individual diastolic left ventricular pressure-volume curves, there were striking quantitative differences. First, the range of volumes over which the left ventricles functioned, and over which these pressure-volume characteristics were observed, varied widely in these subjects. Secondly, the change in filling pressure for a given change in volume varied from subject to subject, with marked differences in the volumes at which the pressure-volume curves changed to become more steep. Finally, a given filling pressure was associated with a wide variation of left ventricular diastolic volume when individual curves were compared.

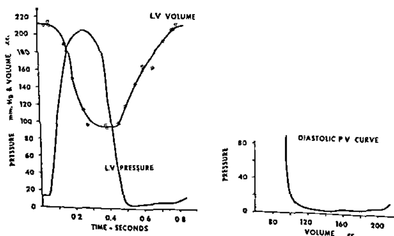


Fig. 3. A representative pressure curve has been constructed from left ventricular pressure recorded during angiocardiography. Calculated volumes have been plotted as circles with respect to time after the onset of QRS. Volume points are connected to form the left ventricular volume curve. The rise in pressure toward end-diastole is due to atrial contraction. On the right, diastolic pressure and volume have been related at corresponding times to form a diastolic pressure-volume curve.

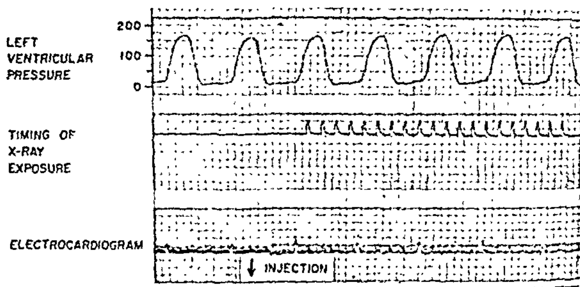


Fig. 2. Recording of x-ray exposure with respect to the electrocardiogram and left ventricular pressure.

polyethylene catheter in the left ventricle or left atrium for recording pressures. In 5 subjects, left ventricular pressures were determined by catheterization of the left ventricle by the retrograde aortic method. Because the volume curves as determined in this study represent a composite of the observations on volume over 3 to 4 beats, a composite pressure curve was also constructed from observations on ventricular pressure during these same 3 to 4 beats when pressures were recorded during filming. When pressures were not recorded during filming, a representative pressure curve was plotted from observations on pressure just prior to filming. In subjects in whom left ventricular pressures were recorded prior to and through the injection and filming periods and in the absence of arrhythmias, it was unusual to observe changes in left ventricular pressure during the period of ventricular filming when compared with pressures recorded prior to the injection of contrast material. The diastolic portion of the cardiac cycle was defined from the pressure curves: the onset of diastole from the point at which left ventricular pressure fell below systemic arterial pressure, and the end of diastole by the sharp rise in ventricular pressure which indicated the onset of ventricular systole.

Brachial arterial pressures were recorded during angiocardiography in all subjects in whom left ventricular pressures were not recorded during filming. Subjects who had marked changes in heart rate, rhythm, or brachial arterial pressure during angiocardiography, and in whom recordings of left ventricular pressure were not made during filming, were not included in this study. In subjects with left ventricular pressure recordings during angiocardiography, the presence of ventricular premature contractions followed by compensatory pauses, or atrial fibrillation with long R-R intervals during filming, occasionally permitted observations of left ventricular pressure and volume over a more prolonged period of diastole and, accordingly, a larger range of volumes and pressures than when the rhythm remained regular. This was the case in curves *B*, *C*, *E*, and *G* of Fig. 4.

Results

From the left ventricular diastolic pressure and volume data, left ventricular pressure and volume were related at corresponding times in diastole, and diastolic left ventricular pressure-volume curves constructed, as illustrated in Figs. 3, 4, and 5. Each of these curves is characterized by an early diastolic portion of iso-

of these factors cannot be determined from this study. However, it is clear that with increasing rates of diastolic filling these other forces would tend to make the pressure-volume curve more steep. However, subjects with valvular insufficiency and the more rapid rates of diastolic filling often had the more flat pressure-volume curves (*D* of Fig. 4, and *B* of Fig. 5), which is consistent with the fact that these factors related to dynamic filling were not critical in determining the differences in the pressure-volume curves observed in this study.

A quantitative comparison of the individual left ventricular pressure-volume curves of these subjects reveals marked differences, which include the range of volumes over which the ventricles functioned and the slopes of the individual curves. The marked differences in diastolic volume in individual curves were not closely reflected by differences in diastolic pressure, and, in a comparison of individual curves, a given diastolic pressure was associated with marked differences in diastolic volume. The differences could not be related to differences in body size, as is evident when end-diastolic pressure is related to end-diastolic volume per square meter of body surface area, as in Table I. Two individuals (*A* and *C* of Fig. 5) with aortic stenosis and left ventricular hypertrophy had higher end-diastolic pressures at lower volumes than did other subjects studied, which suggests that the hypertrophied heart offers a greater resistance to filling. Other individuals had left ventricular diastolic volumes that considerably exceeded normal, yet had filling pressures that were not elevated (*C*, *D*, and *F* of Fig. 4, and *B* and *E* of Fig. 5). The normal left ventricular end-diastolic volume in man by these methods is 100 ± 25 c.c.[28]

By inspection of the individual pressure-volume curves, one can also see a difference in the slopes of the curves. Thus, a given change in diastolic volume bore no fixed relation to a change in diastolic pressure, in a comparison of individual curves. This is more evident if the slopes are analyzed by the calculation of ventricular compliance or coefficient of elasticity.[26] These observations are consistent with the fact that the diastolic left ventricles of these subjects have different elastic properties.

The enlarged left ventricular diastolic volumes with normal levels of filling pressure could have two possible explanations: (1) the pressure-volume characteristics of the normal left ventricle are such that end-diastolic volume may enlarge considerably and not be reflected by an abnormally elevated filling pressure; or (2) the pressure-volume characteristics of the left ventricle are altered by chronic heart disease in man. Because this study was concerned with the pressure-volume characteristics of the diastolic left ventricle of subjects with various types and durations of heart disease, it is difficult from these data to draw conclusions concerning the

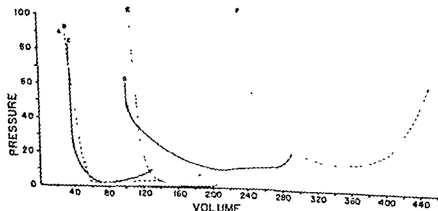


Fig. 5. Diastolic left ventricular pressure-volume curves from subjects on whom data are presented in Table I.

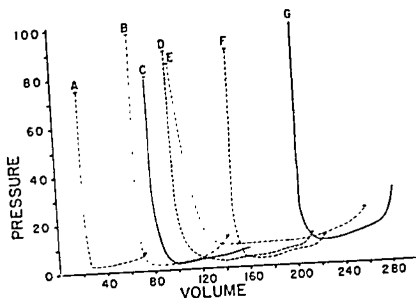


Fig 4. Diastolic left ventricular pressure-volume curves from subjects on whom data are presented in Table 1.

In this regard, 2 of the subjects (*A* and *C* of Fig 5) who had aortic stenosis and evidence of marked left ventricular hypertrophy, as judged by the thickness of the left ventricular wall in the angiocardiograms, showed more elevation of filling pressure at smaller ventricular diastolic volumes than did the other subjects.

Discussion

The shape of the diastolic portion of the left ventricular pressure-volume curve in each of the subjects studied is similar to left ventricular pressure-volume, pressure-segment length, and pressure-circumference curves previously described in experimental animals by others.[3,6,9,10,11-14,22] These curves show little increase in pressure with large increases in volume during the majority of diastolic filling; however, as the ventricle becomes larger, the rises in pressure are greater for a given increase in volume. These data demonstrate that filling pressure and diastolic volume are not linearly related. Near end-diastole in a number of subjects it was possible to demonstrate a break in the pressure-volume curve, in that further small increases in volume were associated with more marked rises in pressure. In fact, it appears from analyzing these curves that the majority of subjects in the recumbent position function at, or very near to, this break in the pressure-volume curve. This suggests that acute elevation of ventricular filling pressure in recumbent subjects may be associated with only small increases in left ventricular volume.

The early portion of diastole in each pressure-volume curve demonstrated a short period during which the ventricular volume began to increase while the ventricular pressure was still falling. The magnitude of the change in volume during this period was largest in subjects with aortic insufficiency or mitral insufficiency associated with an elevated left atrial pressure. That each curve demonstrated a short early diastolic interval of rising volume with falling pressure is consistent with the fact that the early portion of diastole is not an interval of entirely passive filling. It is likely that elastic recoil is playing a role in determining the left ventricular pressure-volume characteristics in this portion of diastole, and this is analogous to what has been termed "ventricular suction" by others.[23,24]

These diastolic pressure-volume curves were determined under dynamic and not static conditions of ventricular filling. Accordingly, in addition to the ventricular elastic properties, viscous, frictional, and inelastic forces are also playing some role in determining the configuration of these pressure-volume curves.[25] The importance

divided into three groups in order to determine the possible effect of the type of disease present on the response to the infusion of acetylcholine. Group I consists of 3 patients with heart disease, Group II consists of 9 patients with cirrhosis, and Group III consists of 9 patients with various diagnoses not primarily cardiac or pulmonary. All patients had regular sinus rhythm, except Patient 2, who had atrial fibrillation. The patients were studied while they were recumbent in the postabsorptive state and without premedication. A No. 8 or No. 9 double-lumen Cournand catheter was passed from an antecubital vein into a main branch of the pulmonary artery, with the proximal lumen in the pulmonary artery approximately 2 cm. beyond the pulmonary valve. In a few instances in which the two lumina openings were rather widely separated the proximal lumen lay in the right ventricular outflow tract. A No. 17 or No. 18 Cournand needle was placed in a brachial artery. Pressures from the arterial needle and the distal lumen of the cardiac catheter in the pulmonary artery were obtained using Statham P23d strain-gauge manometers, and were recorded with either an Electronics for Medicine photographic recorder or a Sanborn Poly-Viso direct-writing instrument. Mean pressures were obtained by electrical or planimetric integration. The zero point for pressure measurements was 10 cm. from the back. Cardiac output was calculated by the Fick principle, with collection of expired air in Douglas bags for 3 minutes and simultaneous sampling of blood from the pulmonary and brachial arteries. After the control measurements of cardiac output and pressures were obtained, freshly prepared acetylcholine chloride (Merck) (1 or 2 mg. per milliliter of normal saline) was infused through the proximal lumen of the catheter, with continuous monitoring of brachial and pulmonary arterial pressures. After a 5-minute period of infusion of

Table I. Physical characteristics of patients studied

Patient	Age (yr.)	Race	Sex	BSA (M.²)	Body weight (Kg.)	Clinical diagnosis
Group I:						
1. C.T.	45	N	M	1.79	72.7	Undiagnosed heart disease with pulmonary hypertension
2. C.L.	32	W	M	1.77	63.2	Myocarditis, atrial fibrillation
3. D.K.	24	N	F	1.53	50.5	Mitral stenosis
Group II:						
4. L.T.	36	W	M	1.79	64.5	Laennec's cirrhosis
5. J.H.	52	W	M	2.17	90.9	Laennec's cirrhosis, chronic lung disease
6. A.N.	28	W	F	1.66	59.1	Laennec's cirrhosis
7. M.H.	44	W	F	1.52	49.5	Laennec's cirrhosis
8. H.P.	35	W	M	1.76	65.9	Laennec's cirrhosis
9. E.M.	43	W	F	1.60	56.4	Posthepatitic cirrhosis
10. T.P.	41	W	M	1.95	79.1	Posthepatitic cirrhosis
11. G.G.	19	W	F	1.42	44.5	Posthepatitic cirrhosis
12. E.J.	51	W	F	1.58	53.6	Porphyria cutanea tarda with cirrhosis
Group III:						
13. M.H.	44	W	M	1.72	60.5	Acute glomerulonephritis
14. J.B.	36	W	M	2.10	99.1	Acute glomerulonephritis
15. N.J.	45	N	F	1.63	59.5	Nephrotic syndrome
16. H.W.	29	N	M	1.58	50.0	Chronic pyelonephritis, multiple vitamin deficiency, and anemia
17. I.J.	47	N	F	1.94	80.5	Unilateral hypertrophy of the extremities
18. J.H.	23	W	M	2.38	111.4	Asymmetrical hypertrophy of the extremities
19. O.J.	42	N	F	1.61	53.2	Essential hypertension
20. E.C.	35	N	F	1.86	75.5	Cerebral arteriovenous aneurysm
21. R.S.	27	N	M	1.81	68.6	Gastrointestinal bleeding of undetermined cause

The effect of acetylcholine upon arterial saturation

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In recent years, numerous studies have been made on the action of acetylcholine upon the pulmonary vasculature. These studies have indicated that acetylcholine is a potent vasodilator of the pulmonary arterioles when there is pre-existing vasoconstriction of these vessels, whether as a consequence of cardiopulmonary disease or of induced hypoxia. More recently, Soderholm and Werkö[1] reported that the infusion of acetylcholine in patients with mitral stenosis may also produce arterial unsaturation. The present study was undertaken to determine whether the infusion of acetylcholine will produce arterial unsaturation in patients with other diseases. Since one possible explanation for the arterial unsaturation produced by acetylcholine is the opening up of anatomic right-to-left pulmonary shunts, we also studied the effects of the administration of 99.6 per cent oxygen upon the arterial unsaturation produced by acetylcholine. Our results indicate that the infusion of acetylcholine into the pulmonary artery may produce arterial unsaturation in patients with diseases other than mitral stenosis, and, in addition, indicate that the unsaturation produced by acetylcholine is largely corrected by the administration of 99.6 per cent oxygen. In addition, other circulatory and ventilatory effects of acetylcholine observed during this study are compared with the findings in earlier studies, most of which have been performed upon patients with either heart disease or pulmonary disease.

Subjects and methods

Twenty-one patients referred for hemodynamic evaluation by the cardiology, renal, and gastrointestinal services of Grady Memorial Hospital were studied. The diagnoses of the patients studied are listed in Table I. The patients have been

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oxygen, which was given by face mask since she felt that she could not tolerate the oral mouthpiece. Her arterial saturation, which originally was normal, fell progressively during the successive periods of study, even while she was receiving 99.6 per cent oxygen. In Patient 14, who had acute glomerulonephritis, there was no apparent reason for the decrease in arterial saturation between the 5 and 10 minutes of administration of oxygen. He also had mild pulmonary hypertension which did not decrease during the administration of acetylcholine, but which did decrease when 99.6 per cent oxygen was administered.

For the entire group of patients there was no significant change in mean oxygen capacity, which averaged 14.8 ml. of oxygen per 100 ml. of blood, both during the control period and during the infusion of the acetylcholine.

B. Cardiac index. The average cardiac index during the control period was 3.71 L. per minute per square meter; during the infusion of acetylcholine the average cardiac index increased to 4.41 L. per minute per square meter (p value < .025, almost .01 exactly). The stroke index during the control period averaged 43.0 ml. per beat per square meter; during the infusion of acetylcholine this increased to 48.9 ml. per beat per square meter (p value < .1, > .05).

C. Heart rate. The average heart rate during the control period was 91.5 beats per minute; during the infusion of acetylcholine the average rate was 95.3 beats per minute (p value > .5). In the 11 patients who were given oxygen, there was a decrease in average heart rate during the administration of oxygen, from 103.4 beats with acetylcholine alone to 99.3 beats per minute (p value < .2, > .1) after 5 minutes of oxygen and acetylcholine, and to 100.6 beats per minute (p value < .2, > .1) after 10 minutes of oxygen and acetylcholine.

D. Brachial arterial pressure. The average brachial arterial mean pressure during the control period was 97.1 mm. Hg; during the infusion of acetylcholine the average was 94.9 mm. Hg (p value < .4, > .3). In the patients who were given oxygen, there was an increase in the average brachial arterial mean pressure during the administration of oxygen and acetylcholine, from an average in these 11 patients of 90.2 mm. Hg during acetylcholine alone to 94.4 mm. Hg (p value < .05, > .025) after 5 minutes of oxygen and acetylcholine, and to an average of 92.5 mm. Hg (p < .4, > .3) after 10 minutes of administration of oxygen during continued infusion of acetylcholine.

E. Pulmonary arterial pressure. The average pulmonary arterial mean pressure during the control period was 23.7 mm. Hg; during the infusion of acetylcholine the average mean pulmonary arterial pressure was 22.9 mm. Hg (p value < .5, > .4). In the 11 patients who were given oxygen while the infusion of acetylcholine was continued, there was a decrease in the average pulmonary arterial mean pressure from 24.5 mm. Hg to 22.9 mm. Hg (p < .4, > .3) after 5 minutes, and to 22.7 mm. Hg (p < .4, > .3) after 10 minutes of combined administration of oxygen and acetylcholine

F. Systemic and pulmonary resistance. The average calculated total systemic resistance decreased from a control value of 1,439 to 1,192 dynes sec. cm.$^{-5}$ during the infusion of acetylcholine (p value < .01). The average calculated total pulmonary resistance decreased from 400 to 313 dynes sec. cm.$^{-5}$ (p value < .02, > .01).

G. Respiratory frequency. During the control period the average respiratory frequency of all patients was 18.1 breaths per minute; during the infusion of acetylcholine the average was 20.7 breaths per minute (p value < .001). The 11 patients who were given oxygen had an average rate of 21.4 during acetylcholine alone, and a decrease to 19.0 (p value < .1, > .05) after 5 minutes of oxygen and acetylcholine and to 19.1 (p value < .4, > .3) after 10 minutes of oxygen and acetylcholine.

H. Ventilation. The average minute volume of expired air during the control period was 7.08 L. per minute, and during the infusion of acetylcholine this increased to 7.93 L. per minute (p value < .05).

I. Oxygen consumption. The average oxygen consumption during the control period was 251 ml. per minute; during

acetylcholine at a constant rate (range 1.60 to 4.00 mg. per minute, average 2.47 mg. per minute, or 20 to 75 μg per minute per kilogram, average 39 μg per minute per kilogram), and during its continued infusion, repeat measurements of cardiac output and of pressures were made.

In 11 patients the infusion of acetylcholine was continued at the same rate, and humidified 99.6 *per cent* oxygen was administered through an oral airway, with occlusion of the nares, or, in a few patients, by face mask. During the fifth to the sixth, and again during the tenth to eleventh minutes of combined administration of acetylcholine and oxygen, measurements were made of pulmonary and brachial arterial pressures, and blood was taken from the brachial artery for analysis for oxygen and carbon dioxide. Measurements of oxygen consumption and blood flow were not made routinely during these periods.

The oxygen and carbon-dioxide content of the blood was determined in duplicate by the methods of Van Slyke.[3] Oxygen capacity was determined in duplicate for each arterial sample. Arterial hemoglobin saturation was calculated after dissolved oxygen was subtracted *from the determinations of arterial oxygen content and from the determinations of arterial oxygen capacity. A factor of 0.3 ml per 100 ml.* of blood was subtracted for dissolved oxygen *from the measurement of oxygen content* when the patients were breathing room air, and a factor of 1.83 ml. per 100 ml. of blood[1] was subtracted when the patients were breathing 99.6 per cent oxygen. The factor for dissolved oxygen subtracted from the determination of oxygen capacity depended upon temperature and barometric pressure.[4] The amount of oxygen and carbon dioxide in expired air was determined in duplicate, using a Scholander microanalyzer.[6]

The statistical significance of the changes noted were evaluated by the "t" test.[7]

Results

Table II gives the circulatory, respiratory, and blood gas data obtained before the infusion of acetylcholine, during the infusion of acetylcholine, and during the infusion of acetylcholine with concurrent administration of 99.6 per cent oxygen for 5 and for 10 minutes. Table III summarizes the changes in mean arterial saturation for all patients studied during each period of study and also tabulates the mean changes in each group of patients. Unless otherwise stated in the results and discussion, *the average values reported refer to the averages of all patients in each particular study group.*

A. Brachial arterial saturation. The average arterial saturation during the control period for all patients was 94.9 per cent, there was no significant difference between the averages of the three groups of patients. During the infusion of acetylcholine, the average arterial saturation for all patients decreased to 88.1 per cent (p value $< .001$), and there was no significant difference between the average responses of the three groups of patients. The one patient (Patient 2) who actually increased his arterial saturation during the infusion of acetylcholine had moderate hyperventilation, which may have altered his response. In the 11 patients who were studied during the continued infusion of acetylcholine with the administration of *99.6 per cent oxygen, there was an increase from an average saturation of 89.3 per cent with acetylcholine alone to an average arterial oxygen saturation of 94.9 per cent* (p value $< .05$) *after 5 minutes of oxygen* and acetylcholine, and to an average *arterial oxygen saturation of 94.1 per cent* (p value $< .05$) *after 10 minutes of oxygen* and acetylcholine. *In most instances no* further increase in arterial saturation occurred between 5 and 10 minutes of administration of 99.6 oxygen during concurrent administration of acetylcholine. In several instances, notably Patients 7 and 14, there was an unexplained significant decrease in arterial saturation during this interval. Patient 7, who had Laennec's cirrhosis, had marked tachypnea and hyperventilation during periods A and B, with a ventilatory equivalent for oxygen (liters inspired air per 100 ml. of oxygen consumed) of 5.97 during infusion of acetylcholine in period B, during which she did not become significantly unsaturated. Her respiratory rate decreased to 26 per minute after 5 minutes of oxygen, and to 20 per minute after 10 minutes of

and during infusion of acetylcholine with concurrent administration of 99.6 per cent oxygen

f	$\dot{V}_E$	$\dot{V}_{O_2}$	VE	R_E	Blood gases			
					Ca_{O_2}	Ca_{O_2}-$C\bar{v}_{O_2}$	Ca_{CO_2}	CAP_{O_2}
18	6.43	278	2.34	.71	16.96	8.19	21 8	18 87
24	10.85	385	2.84	.81	16.07	7.54	21 3	18 98
26					19.65		21 9	18 83
32	10.56				20.05	10.80	21.1	19 17
18	10.03	300	3.36	.81	21 70	7.47	16 2	22.90
22	9.59	274	3.51	.86	21.71	7.82	16 0	22.06
17					23 21		16 0	22.85
17					23.36		17 2	22 41
19	5.35	202	2 68	71	14 47	4 99	18 4	15 56
20	7 43	235	3.19	.77	12 95	5 33	17 8	15.94
15	5 08	201	2 56	.81	16 68	6.52	21 9	18 16
19	6 23	215	2 92	83	15 32	4 18	22 5	18 01
15	4 29	243	1.80	.68	14 67	4 11	26 0	16.92
15	5.23	265	2 00	.72	13 94	4 11	26 0	17 02
24	9 59	349	2 77	83	11 49	2 30	19 8	11 77
30	8 59	303	2 86	.74	11 67	2 29	20 3	12 80
33					13 63		20 9	12 66
26					13 69		20 9	12 91
33	17.33				13 84	4 54	19 0	14.22
39	15 57	261	5 97	1 03	13 78	4.71	17 4	14 73
26					15 28		19 7	15 05
20					14 06		20 3	14 48
17	7 47	197	3 81	.80	8 76	2 23	20 6	10 00
20	8 67	255	3.43	75	8 41	1 85	20 8	10.41
18					10 86		20.7	10 62
19					10 98		20 6	10.77
13	5 14	182	2 85	74	13 90	2 86	21 0	14.67
19	7.11	262	2 65	.82	13 97	3 27	20 6	15 05
13					15 50		21 8	15.27
11					15 81		21.7	15.04
13	6 07	248	2 46	.85	12 67	2 05	19 9	12.61
15	7 61	277	2 76	85	11 16	1 92	20 0	12 86
14					14 02			13.17
13					14 13			13 75
14	4 77	242	2 00	70	14 61	3.31	20 6	15.56
19	5 98				13 13	2 48	20.1	15.74
16					15 65		20 8	15.56
22					15 58		20.7	14.75
16	4.50	189	2 41	70	14.16	4 59	20.9	15.30
16	6.29	191	3.31	.80	13 78	4.32	20 9	15.45
19	7.14	225	3.20	76	12.71	3 52	20.1	13.81
19	7.44	220	3.40	.83	11.40	2.05	20 0	13.88

Table II. Circulatory, respiratory, and blood gas data before and during infusion of acetylcholine,

Patient	Period of study	Ach (μg/Kg./min.)	Sa_{O_2}	CI	HR	Pressures (mm. Hg) BA (s/d m)	Pressures (mm. Hg) PA (s/d m)
Group I.							
1.	A	0	91.3	1.90	100	116/73 (95)	123/48 (73)
	B	33	86.0	2.85	100	137/85 (109)	113/43 (72)
	C	33	98.0		94	132/91 (110)	98/38 (61)
	D	33	98.3		100	130/89 (108)	98/38 (61)
2.	A	0	96.1	2.27	123	121/85 (100)	42/28 (33)
	B	55	100.0	1.98	111	136/79 (98)	43/24 (30)
	C	55	96.3		112	121/81 (96)	42/23 (33)
	D	55	98.9		119	122/82 (97)	43/23 (33)
3.	A	0	95.4	2.65	120	114/74 (92)	79/39 (64)
	B	48	83.1	2.88	130	119/77 (95)	84/46 (68)
Group II.							
4	A	0	93.5	1.72	80	102/67 (85)	14/0 (8)
	B	31	86.5	2.87	78	102/67 (79)	16/1 (7)
5	A	0	88.3	2.72	69	158/88 (118)	43/19 (30)
	B	30	83.3	2.97	67	150/86 (126)	29/13 (19)
6.	A	0	100.2	9.14	120	109/59 (83)	22/9 (18)
	B	37	93.1	7.97	140	115/70 (93)	29/16 (25)
	C	37	97.8		130	115/67 (91)	33/12 (24)
	D	37	96.3		134	103/67 (85)	24/16 (20)
7.	A	0	99.4		107	141/79 (105)	19/7 (9)
	B	32	95.4	3.65	99	131/71 (101)	18/7 (12)
	C	32	93.1		85	165/81 (113)	18/9 (12)
	D	32	88.1		89	157/81 (111)	19/9 (13)
8.	A	0	89.7	5.02	90	118/46 (74)	19/11 (16)
	B	33	82.3	7.83	108	103/43 (68)	24/15 (18)
	C	33	89.8		114	103/45 (69)	25/14 (21)
	D	33	89.6		108	91/43 (68)	21/11 (19)
9.	A	0	96.5	3.98	92	136/73 (96)	17/8 (13)
	B	46	94.3	5.00	93	129/73 (96)	14/10 (12)
	C	46	92.9		100	126/68 (95)	15/11 (13)
	D	46	96.5		96	125/66 (93)	16/8 (10)
10.	A	0	103.2	6.20	85	103/69 (79)	23/14 (18)
	B	33	88.8	7.40	95	101/33 (53)	22/11 (16)
	C	33	97.2		87	113/41 (59)	14/4 (9)
	D	33	93.8		89	97/43 (53)	23/13 (17)
11.	A	0	96.0	5.15	111	104/66 (78)	17/8 (12)
	B	58	85.0		119	105/63 (77)	23/11 (16)
	C	58	92.8		118	105/63 (81)	21/11 (15)
	D	58	97.6		114	105/64 (81)	21/9 (15)
12.	A	0	94.5	2.61	81	125/84 (100)	26/12 (17)
	B	52	90.7	2.80	83	125/68 (92)	19/7 (11)
Group III:							
13.	A	0	94.1	3.72	55	181/83 (121)	34/14 (23)
	B	40	83.6	6.24	56	136/71 (103)	33/13 (21)

For footnotes and continuation of Table II, see pages 518-519.

					Blood gases			
f	$\dot{V}_E$	$\dot{V}_{O_2}$	VE	R_E	Ca_{O_2}	Ca_{O_2}-$C\bar{v}_{O_2}$	Ca_{CO_2}	CAP_{O_2}
11	10 36	390	2 68	.80	13 83	3 94	20 5	15 13
13	10 06	371	2.74	.75	12 57	3 74	21 3	15 20
12					15 92		21 1	14 98
12					15 02		21 6	15 34
26	5.77	147	3 94	.87	9 63	4 27	13 9	11 05
30					8 98		13 2	11 38
20	5 38	197	2 77	66	8 04	4 75		8 49
21	6 07	197	3 13	.54	7 60	3 19		8 62
20	4.56	180	2 56	75	14 64	2 54		15 78
22	5 68	194	2 95	75	12 80	2 84		15 73
15	12 03	434	2 78	89	18 95	4 74	18 0	19 94
15	8 79	350	2 53	77	18 19	4 03	17 1	19 31
15					19 96		18 5	19 19
16					19 68			19 12
16	4 12	205	2 05	61	12 56	3 90		13 77
17	4 88	246	2 03	57	11 99	3 60		13 86
20	5 51	231	2 41	74	15 71	5 56	20 0	16 89
19	8 87	239	3 72	92	15 34	6 24	18 3	16 89
18	6 51	265	2 48	79	9 69	3 24	20 0	10 54
20	7 70	329	2 37	73	8 94	2 79	18 7	11 10
19					11 42		19 0	11 19
22		343†			11 37	2 66	19 6	11 26

D. During acetylcholine infusion with 99 6 per cent oxygen for 10 minutes. Ach: Acetylcholine (µg. Kg./min.) Sa_{O_2}. Arterial satu- ø Systolic. d Diastolic. m Mean f Respiratory frequency breaths per minute. $\dot{V}_E$. Expired air, liters per minute, BTPS $\dot{V}_{O_2}$- consumed R_E. Respiratory exchange ratio. Ca_{O_2}. Arterial oxygen content, ml per 100 ml blood Ca_{O_2}-$C\bar{v}_{O_2}$ Brachial artery minus Arterial blood oxygen capacity, ml per 100 ml blood.

average of 19.4 mEq. per liter during acetylcholine alone and an increase to 20.0 mEq. per liter (p value < .025, > .01) after 5 minutes of oxygen and acetylcholine, and to 20.4 mEq. per liter (p value < .05, > .025) after 10 minutes of oxygen and acetylcholine.

Symptoms. Few of the patients were symptomatic during the infusion of acetylcholine. However, several complained of tightness of the chest and coughing, and one patient raised a moderate amount of pharyngeal secretions. One patient (not included in this report) with accelerated hypertension and congestive heart failure who had elevated "pulmonary capillary" pressure at rest developed marked dyspnea and orthopnea acutely on several occasions during the infusion of less than 1 mg. of acetylcholine into the main pulmonary artery.

Discussion

During the infusion of acetylcholine at an average rate of 2.5 mg. per minute or 39 µg per minute per kilogram a decrease in arterial saturation occurred in all but one of the patients studied. This finding was not noted in man [illegible] studi[illegible] human beings, perha[illegible]

Table II. Cont'd

Patient	Period of study	Ach (μg/Kg/min.)	Sao₂	CI	HR	Pressures (mm. Hg)	
						BA (s/d m)	PA (s/d m)
14.	A	0	93 1	4 71	105	145/87 (111)	44/19 (36)
	B	20	84 0	4 72	105	145/101 (121)	43/29 (37)
	C	20	97 9		108	145/106 (124)	28/21 (24)
	D	20	89 6		101	144/101 (121)	24/20 (22)
15	A	0	89 2	2 11	97	133/57 (77)	29/10 (17)
	B*	34	80 5		106	102/59 (67)	37/11 (23)
16.	A	0	98 1	2 63	118	130/100 (118)	42/16 (25)
	B	41	91 2	3 91	109	112/93 (115)	44/11 (26)
17.	A	0	91 5	3 65	82	98/68 (80)	30/16 (22)
	B	27	82 6	3 52	81	108/72 (88)	12/10 (10)
18.	A	0	96 7	3 85	65	134/76 (97)	34/14 (25)
	B	22	95 9	3 65	68	123/82 (101)	29/9 (17)
	C	22	97 7		56	136/87 (107)	32/14 (22)
	D	22	96 6		54	127/82 (101)	33/14 (22)
19.	A	0	93 0	3 26	73	218/116 (156)	27/5 (12)
	B	75	88 1	4 24	83	218/118 (162)	20/5 (11)
20	A	0	94 8	2 23	74	110/74 (83)	25/10 (14)
	B	33	92 6	2 06	70	100/52 (74)	20/8 (14)
21.	A	0	91 8	4 52	75	126/73 (91)	24/9 (12)
	B	38	82 6	6 51	100	119/59 (75)	26/9 (15)
	C	38	90 8		88	137/71 (93)	29/12 (18)
	D	38	89 7	7 12	103	141/71 (96)	33/12 (18)

*Patient felt hot and wanted to sit up.

†*Collins respirometer measurement*

Abbreviations. A: Control B: During acetylcholine infusion C. During acetylcholine infusion with 99 6 per cent oxygen for 5 minutes. ration, per cent CI Cardiac index (L./sq M./min.). HR: Heart rate (beats/min.). BA: brachial artery. PA: Pulmonary artery. *Oxygen consumption, ml per minute, STPD VE Ventilatory equivalent for oxygen, liters inspired ventilation per 100 ml oxygen* pulmonary artery oxygen con ent, ml per 100 ml. blood C_{aCO_2}: Arterial carbon-dioxide content, ml. per 100 ml blood CAPo₂

the infusion of acetylcholine this increased to 267 ml. per minute (p value > .6).

J. Ventilation equivalent. The average ventilation equivalent for oxygen during the control period was 2.66 L. of inspired air per 100 ml. of oxygen consumed; during the infusion of acetylcholine the average increased to 2.91 L. of ventilation per 100 ml. of oxygen consumed (p value < .4, > .3).

K. Respiratory exchange ratio. The average respiratory exchange ratio during the control period was 0.76; during the infusion of acetylcholine the average was 0.78 (p value < .4, > .3).

L. Arteriovenous oxygen difference. The average difference in oxygen content between the brachial artery and the pulmonary artery during the control period was 42.7 ml. per liter of blood; during the infusion of acetylcholine the average value was 39.2 ml. per liter of blood (p value < .1, almost 0.05 exactly).

M. Brachial arterial carbon-dioxide content. The average arterial carbon-dioxide content during the control period was 19.9 mEq. per liter; during the infusion of acetylcholine the average was 19.6 mEq. per liter (p value < .1, > .05). The patients who were given oxygen had an

also that acetylcholine increased the number of large microspheres which passed through the pulmonary circulation in the dog.[31] It should be noted in the present study that the arterial hemoglobin saturation during the administration of oxygen was calculated using an assumed value of 1.83 ml. per 100 ml. of blood for dissolved oxygen in arterial blood. In any individual patient, this figure may have been slightly low or high. To study the presence of small right-to-left shunts while the subject is breathing 99.6 per cent oxygen it would be preferable to measure arterial oxygen tension, since changes in arterial saturation are relatively insensitive at this portion of the oxygen hemoglobin dissociation curve. The development of alveolar transudation secondary to an increase in capillary permeability cannot be excluded, although there is little evidence to support this hypothesis. Severe bronchiolar constriction might lead to systemic arterial unsaturation, but wheezing was not heard in any of our subjects and has not been mentioned by other workers. Bishop and associates[32] studied the effects of infusing acetylcholine (2.0 mg. per minute) into the right atrium of 12 patients with mitral stenosis who were breathing 45 to 50 per cent oxygen, both at rest and during exercise. With the patients at rest, they found that acetylcholine produced no significant changes in the mean values of alveolar or arterial oxygen tension, alveolar-arterial oxygen difference, or ratio of physiologic dead space to tidal volume. During exercise by the patients, they found that acetylcholine produced a slight decrease in the mean alveolar-arterial oxygen difference, instead of the slight increase which occurred during exercise without acetylcholine. In their analysis of the individual responses, however, they noted that when the patients were breathing 45 to 50 per cent oxygen, both at rest and during exercise, acetylcholine did tend to produce a greater decrease in alveolar-arterial oxygen difference in patients with a high control resting value for pulmonary arterial pressure, in patients with a high ratio of dead space to tidal volume, and in patients with a high alveolar-arterial oxygen difference. Physiologic dead space tended to decrease in patients who had higher pulmonary arterial pressure, and to increase in patients in whom pressure was less elevated. They did not believe that the effects were produced by the action of acetylcholine on the airways because acetylcholine is so rapidly destroyed before reaching the systemic circulation, and because they observed no changes in total pulmonary ventilation or respiratory frequency, or alterations in the amplitude of the respiratory variation in the pulmonary wedge pressure during the infusion of acetylcholine. They observed no effects by acetylcholine, when the patients breathed 45 to 50 per cent oxygen, upon cardiac output, oxygen uptake, arterial-venous oxygen difference, mean brachial arterial pressure, or pulse rate, either at rest or during exercise. They related the different actions of acetylcholine at different stages of mitral stenosis to two overlapping processes. The first process is a maldistribution of ventilation, present to some extent at all stages, in which the compensatory vasoconstriction which occurs in underventilated areas is released by acetylcholine, causing an increase in physiologic dead space and alveolar-arterial oxygen difference. As the disease progresses, the second process, a primary maldistribution of blood, becomes more important. In these circumstances, however, acetylcholine was thought to increase local blood supply in parts of the lung irrespective of local ventilation and alveolar oxygen tension, with a resultant decrease in dead space and alveolar-arterial oxygen difference. They thought that the change from a predominance of maldistribution of air to a predominance of maldistribution of blood in mitral stenosis occurred with a mean pulmonary arterial pressure of about 40 mm. Hg

A possibly significant decrease in mean pulmonary arterial pressure was observed in only a few subjects in the present study, but the average change was not striking, although previous workers[2,8-11,17,33,34] have noted more striking decreases in pulmonary arterial pressure, particularly when the pressure is elevated and when there are not very severe irreversible pulmonary vascular changes present. However, it should be emphasized that, in contrast to most previous studies, in which most of

Table III. Summary of changes in mean arterial saturation

Period of study	All patients n = 21	Patient group I n = 3	Patient group II n = 9	Patient group III n = 9
A	94.9	94.3	95.7	94.3
B	88.1**	89.7	87.7**	86.3**
C	94.9*	97.2	93.9	95.5
D	94.1*	98.6	93.6	92.0

* = p value < .05
** = p value < .001

Significance of changes evaluated for changes between study periods A-B, B-C, and B-D using only data from those patients in each group studied in both periods considered.

ences in experimental protocol in some studies, i.e., administration of acetylcholine at lower rates of infusion[8,9] or administration in single doses,[10-12] although Wood,[13,14] employing an ear oximeter and using single doses of acetylcholine injected into the pulmonary artery of patients with heart disease, did observe a fall in arterial saturation, particularly in patients with cor pulmonale. Cournand and associates,[15] in studies in which one lung was breathing 16 per cent oxygen while the other breathed 21 per cent oxygen, found that the infusion of acetylcholine at a rate of 1 to 4 mg. per minute into either pulmonary artery caused an increase in the blood flow to the hypoxic lung and a decrease in arterial saturation. In subsequent studies, Fritts and associates[9] noted that infusion rates of acetylcholine of 0.5 mg. per minute did not produce a decrease in arterial saturation while the subjects breathed 21 per cent oxygen, but they did observe that when the subjects were breathing 12 per cent oxygen, infusion of acetylcholine decreased the average oxygen arterial saturation from 74 to 71.5 per cent. Söderholm and Werkö[2] found that the infusion of acetylcholine at a rate of 3 to 14.5 mg. per minute into the pulmonary artery of patients with mitral stenosis produced arterial unsaturation, and believed that this was due to dilation of pulmonary vessels in poorly ventilated areas, producing a shift in the pulmonary ventilation-perfusion ratio. Niden and associates[16] observed in dog studies that the infusion of acetylcholine produced a decrease in arterial saturation, and that the effect was reduced but not eliminated by controlling the volume of ventilation or by the inhalation of 25 or 30 per cent oxygen. They concluded that changes in the ventilation-perfusion ratio were of major importance, and that acetylcholine, in addition, produced local physiologic or anatomic intrapulmonary shunting of blood. Chidsey and associates[17] have recently found that the infusion of acetylcholine at a rate of 3 mg. per minute into the right atrium of patients with pulmonary emphysema lowered the arterial saturation in 9 of the 13 patients studied. They thought that this effect was best explained by presuming that acetylcholine dilated vessels constricted by hypoxia, thus increasing the perfusion of poorly ventilated areas of the lungs.

The findings in the present study indicate that acetylcholine when infused at moderate rates produces arterial unsaturation in patients with heart disease, in patients with cirrhosis, and in patients without functional or structural disease of the heart and lungs. The most likely explanation appears to be that acetylcholine blocks the local protective vasoconstriction which normally helps to maintain a normal arterial saturation by decreasing perfusion to poorly oxygenated areas of the lung.[18-28] The slight degree of arterial unsaturation considered to be normal[4,29] perhaps results in part from this local vasoconstrictive mechanism not functioning perfectly in all areas, although other factors, such as Thebesian veins draining into the left atrium or bronchial venous blood draining into pulmonary veins, are possible contributing factors.[30] An alternate explanation for the arterial unsaturation produced by acetylcholine is that acetylcholine opens up actual pulmonary arteriovenous shunts; the correction of the systemic arterial unsaturation with 99.6 per cent oxygen is evidence, albeit not absolute, against this hypothesis, although the fact that the administration of 99.6 per cent oxygen did not raise the oxygen saturation to 100 per cent, even in the patients without liver disease, makes it difficult to exclude this possibility completely, and it has been recently reported

there was also a tendency toward a slight decrease in the carbon-dioxide content of the brachial artery, possibly reflecting the tendency to increased ventilation; however, the observed changes were only questionably statistically significant.

Summary

1. Infusion of acetylcholine into the pulmonary artery or right ventricular outflow tract in a dose of 1.6 to 4.0 mg. per minute (20 to 75 μg per minute per kilogram) in the patients studied was associated with the following changes: (a) a decrease in mean arterial saturation; (b) an increase in mean cardiac index and a decrease in mean calculated total pulmonary resistance and total systemic resistance but no significant change in mean pulmonary arterial pressure, mean brachial arterial pressure, or mean pulse rate; (c) a slight increase in minute ventilation, with no significant change in mean oxygen consumption or respiratory exchange ratio and no statistically significant increase in mean ventilation equivalent.

2. Inhalation by the patient of 99.6 per cent oxygen for 5 minutes while acetylcholine was being infused reversed the arterial unsaturation produced by the infusion of acetylcholine, but 5 or 10-minute periods of breathing oxygen during the infusion of acetylcholine did not usually produce a full 100 per cent oxygen saturation of arterial hemoglobin.

3 The mechanism of the systemic arterial oxygen unsaturation produced by acetylcholine is discussed, and it is assumed that acetylcholine produces arterial unsaturation by decreasing the protective local vasoconstriction which is thought to occur normally in areas of the lung which are poorly ventilated.

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the patients had elevated pulmonary arterial pressure, only a few patients in the present series had initially elevated pulmonary arterial pressure, and Fritts and associates,[9] in studies employing infusion rates of 0.5 mg. per minute, have shown that the lowering of pulmonary arterial pressure was considerably greater in the same patients after elevation of pulmonary arterial pressure had been produced by hypoxia. Harris[11] noted that acetylcholine produced a decrease in pulmonary arterial pressure if there was moderate (50 to 75 mm. Hg) pulmonary hypertension, but that this effect was much less likely to occur if the initial pulmonary arterial pressure was normal or if there was severe pulmonary vascular disease present. It would appear both from previous studies and from the present study that the vasodilatory action of acetylcholine on the pulmonary vessels of human beings at the doses employed is more potent than the possible pulmonary pressor effect which results from the slight arterial unsaturation produced either by the acetylcholine itself or by the simultaneous breathing of low concentrations of oxygen.[9,25] It would appear from the present study that infusion of acetylcholine can produce changes in the pulmonary vasculature of a degree which produces detectable arterial unsaturation without a significant detectable decrease in mean pulmonary arterial pressure, and with only a slight decrease in calculated mean total pulmonary resistance, whether or not these values are elevated by preexisting heart or pulmonary disease.

Although early animal studies, most of which employed the isolated perfused lungs of animals, indicated that acetylcholine produced predominantly pulmonary vasoconstriction,[35-41] subsequent studies have indicated that acetylcholine may also produce results which can be interpreted as vasodilatation of the pulmonary vessels, and that whether vasoconstriction or vasodilation is inferred from individual studies depends upon the species of animal studied and the net effect of possibly opposite reactions to different doses of acetylcholine upon the pulmonary arterioles and pulmonary venules.[42-50] However, Johnson, Hamilton, Katz and Weinstein[51] and, later, Friedberg, Katz and Steinitz[52] concluded that the production of pulmonary vasodilation or vasoconstriction after the administration of acetylcholine played an unimportant role in varying the pulmonary arterial pressure, which they thought was affected mainly by the indirect effects of acetylcholine. Borst, Berglund and McGregor[53] also found inconsistent pulmonary vasomotor effects of small magnitude if increases in transpulmonary pressure were prevented. In general, however, the majority of animal studies have indicated that a small dose of acetylcholine produces vasodilatation, and a large dose produces vasoconstriction of the pulmonary vessels in animals.

A significant increase in cardiac output was noted in our subjects during the infusion of acetylcholine. Although an increase in cardiac output was not found in most previous studies, some workers[2,13,17] have also noted occasional slight increases in cardiac output; in the present study this increase may be related to the arterial unsaturation.

No significant effect upon heart rate was observed in the patients of the present study or in most patients studied by others.

Little effect on systemic arterial pressure was noted during the infusion of acetylcholine into the pulmonary artery at the rates employed in this study. This lack of systemic effect is similar to the results of others and is presumably due to the rapid inactivation of acetylcholine in the blood stream.[54]

A statistically significant increase in ventilation without a significant increase in oxygen consumption, reflected in a slight average increase in ventilation equivalent, was noted during the infusion of acetylcholine in our subjects as in those studied by Soderholm and Werkö.[2] However, most other workers have not observed significant increases in either ventilation or oxygen consumption, and it is possible that the increased ventilation observed in the present study was due to the degree of arterial unsaturation, the diseases of the patients studied, differences in experimental design, anxiety of the patients, or technical errors. In the present study, during the infusion of acetylcholine

Isometric contraction and contractility in the intact mammalian ventricle

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Considerable attention has been given to the measurement of the maximum tension developed during isometric contraction of the cardiac muscle as an index to myocardial contractility or physiologic fitness. Such studies have included measurements of segments of muscle attached to various lever or arch systems[2] and measurement of the pressure generated during isovolumetric contractions of the entire ventricle.[3] Other studies have emphasized the importance of the integral of tension with respect to time as an index to energy liberated by myocardial contraction. These investigations are exemplified by the recent studies of Sarnoff and his colleagues[4] which show an impressive correlation between the time integral of ventricular pressure (the tension time index) and myocardial oxygen consumption. Still other investigators, including Frank,[5] Starling,[6] and Wiggers[7] among the first, have emphasized the usefulness of measurements of the rate of tension or pressure development as a guide to changes in myocardial contractility. In previous studies in this laboratory a linear relationship has been found between the maximal rate of pressure development in the ventricle during the phase of isometric contraction and the end-diastolic circumference of the ventricle at any given state of myocardial contractility, and between the rate of pressure development and the contractile force of the ventricle recorded by a Walton strain-gauge arch at any given end-diastolic circumference. An excellent correlation was found between the rate of pressure development and the product of the contractile force and the end-diastolic circumference of the ventricle, under experimental conditions in which both circumference and contractility were altered.[8] This product predicts the tension of isovolumetric contraction of the ventricle. We, therefore, postulated that the rate of tension development will maintain a predictable relationship to the maximum tension developed during isometric contraction as either the fiber length or myocardial contractility is changed. It was also suggested that a useful measure of contractility might be obtained by the measurement of the rate of change of tension considered in relation to the end-diastolic stretch of the muscle. The purpose of the present investigation was to explore the interrelationships between fiber length and the various functions of myocardial isometric contraction

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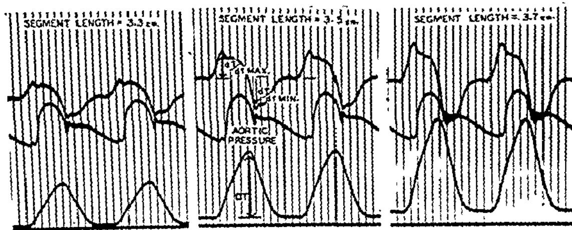


Fig. 1. These tracings show (*from above downward*) the time derivative of tension, the aortic pressure, and the isometric tension registered by a strain-gauge arch sutured to the anterior wall of the left ventricle of a thoracotomized dog. The maximal amplitude of the derivative is proportional to the steepest slope of the tension curve (dT/dt Max), whereas the area under the systolic portion of the tension curve is the integral of tension with respect to time (T.I.T.). From left to right, the changes induced by increasing the distance between the legs of the arch and thereby the stretch of the muscle segment may be seen. The amplitude of both the developed tension curve (D.T.) and of its derivative are increased without any apparent alteration of their time course. The duration of contraction, the time to dT/dt Max, the time to peak tension, and the time to dT/dt Min (most negative portion of the derivative) are all unchanged by an increase in fiber stretch.

ohm resistor and a .02-microfarad condenser, yielding a time constant of 0.66 millisecond. The amplitude response was determined by recording simultaneously an electrically generated sine wave and its derivative as obtained by this circuit. The amplitude of the differentiated sine wave was proportional to the known slope of the original signal to beyond 80 cycles per second. No phase distortion at these frequencies could be detected by standard oscilloscopic analysis. Of greater concern, however, is the possible influence of the muscle surrounding the sample not attached to the arch. This influences to an extent the shape of the curve during ejection of the ventricle. Preliminary studies showed that the time course and magnitude of the tension curve recorded by the strain-gauge arch is altered, but only slightly, by sudden ligation of the aorta in diastole, which greatly alters the tension produced by the adjacent muscle during the subsequent beat. Since these studies included a wide variety of physiologic conditions, including altered end-diastolic volume, heart rate and contractility, the possibility of an important influence of the adjacent muscle upon the parameters measured in this study is thought to be minimal. Similar results have previously been reported by Cotten[9] for left ventricular outflow constriction, even when

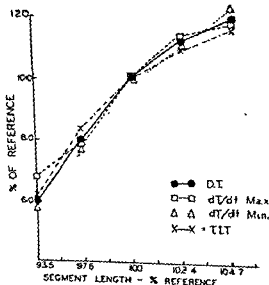


Fig. 2. The proportionality and parallelism of the changes in the various functions of isometric contraction as segment length is altered in a representative experiment may be seen. Abbreviations are the same as in Fig. 1.

at varying states of myocardial contractility in view of these hypotheses.

Methods

The tension generated during isometric contraction of segments of left ventricular myocardium of 10 thoracotomized dogs was sensed by a modification* of the Walton-Brodie strain-gauge arch.[7] This instrument was sutured firmly to the anterior wall of the ventricle with the legs of the arch approximately 3 cm. apart. Measured increments of the length of the arch and the attached cardiac muscle were then induced by turning a threaded bolt. The tension signal was differentiated electrically, yielding a continuous record of the time derivative of tension. The greatest amplitude of the derivative is proportional to the steepest slope of the tension curve. Planimetric integration was used to obtain the area of the tension curve (the time integral of tension).

The animals were anesthetized with intravenous pentobarbital, 10 to 12 mg. per kilogram, and morphine sulfate, 2 mg. per kilogram, and ventilated via a cuffed endotracheal tube. A left thoracotomy was performed, the pericardium was opened, and the strain-gauge arch was sutured to the lateral wall of the left ventricle. The heart rate was controlled by electrical pacing via fishhook electrodes in the outflow tract of the right ventricle, with simultaneous stimulation of the cardiac end of the cut vagus nerve. The ventricular site for pacing was utilized because of difficulty in achieving a slow, steady rate when pacing was done from the atria with background vagal stimulation. Although ventricular function is altered by this procedure, it was a constant alteration in each of the experiments. As such, it should not prejudice the comparison of the results of the specific interventions on the parameters recorded in this study. The tension, the derivative of tension, and the aortic pressure were recorded at each of 4 to 8 different lengths of the arch. These initial measurements were carried out without drugs other than the anesthetic and will be referred to as the control condition. The length of the muscle at which a 0.5-mm. increment in length resulted in a measurable increase in the diastolic tension under control conditions was taken as the minimal isometric length. After the control studies were completed, the contractility of the myocardium was increased by a steady infusion of epinephrine (1 mg./100 ml.) adjusted so as to maintain a marked increase in aortic pressure without ventricular arrhythmias. After a reasonably steady state was obtained, the parameters were again recorded at each of the segment lengths utilized in the control series. After a period for recovery, quinidine sulfate (10 mg. per kilogram) was injected intravenously, and the stretch series was repeated after a noticeable decline in aortic pressure and the tension developed by the strain gauge at a constant fiber length was observed.

Since the tension recorded by the strain-gauge arch is influenced by the variable size of the sample of muscle included by the sutures, comparison of absolute levels of tension between different animals is not meaningful. Therefore, the analysis of the various functions of tension was based on percentage changes. A reference contraction for each animal was selected during the control conditions. The contraction selected was that one most nearly at the midpoint of the stretch series. The amplitude of each of the measured parameters of contraction, developed tension (D.T.), the maximum rate of tension development (dT/dt Max), maximum rate of tension decline (dT/dt Min), and the time integral of developed tension (T.I.T.) for this contraction was taken as 100 per cent. All other measurements of the variables during the control period and the epinephrine and quinidine experiments are expressed in relation to this reference contraction.

The characteristics of the strain-gauge arch employed in these studies has been reviewed in detail by Walton[8] and Cotten.[9] The amount of shortening of the arch at the maximal tensions generated by the sample of muscle has been shown to be slight (approximately .007 of the initial length). The frequency response of the gauge is essentially flat to above 15 cycles per second. The differentiator employed consists of an R-C circuit using a 33 kilo

*Made by O. J. Brodie, Department of Pharmacology, Medical College of South Carolina, Charleston, S. C.

and reproducible length tension curves, active and passive, could be obtained, although a slight tendency for minimal changes of the same kind persisted. The major changes in this direction occurred with the first stretch series, and there were progressively smaller changes upon succeeding repetitions. Therefore, since the major purpose of these experiments was to compare the interrelationships between the various contraction parameters, fiber length, and alterations of the inotropic state, the experiments considered in detail were limited to those in which the total increase in fiber length did not exceed 25 per cent. Such an increase in fiber length would result in an increase in ventricular volume of approximately 100 per cent (assuming a spherical cavity). Since changes of such magnitude are rarely, if ever, acutely engendered by normal or pathologic variation in the mammalian circulation, these studies probably encompass the physiologically important range. An example of the effect of stretch upon the developed tension and the derivative and integral of tension is shown in Fig. 1.

Fig. 2 shows the parallelism of the increase of various functions of contraction in one representative experiment as the length of the sample of muscle was increased. It is obvious that each of the parameters measured, i.e., the developed tension (D.T.), the maximum rate of tension development (dT/dt Max), the maximum rate of tension relaxation (dT/dt Min), and the time integral of developed tension (T.I.T.), are increased in approximately proportional fashion with increases in fiber length. Similar results were obtained in all the experiments in all of the dogs.

The extent of the parallelism of the changes in the contraction parameters was investigated by comparing changes in D.T. with changes in dT/dt Max, dT/dt Min, and T.I.T. Since the measurements were all expressed as a percentage of a standard or reference contraction, it was possible to lump data from the analogous experiments in all of the dogs and to analyze these relationships with standard statistical methods.

In Fig. 3,*A* the relationship between D.T. and dT/dt Max when only the contraction length of the sample of muscle was altered is displayed. A very striking correlation between these variables was found ($r = .981$), demonstrating the proportionality of the changes of both variables to changes in fiber length. However, these changes were not precisely parallel, as shown by the slope of the regression of dT/dt Max on D.T. The rate of increase of dT/dt Max was .933 that of the increase of D.T., a difference which, although slight, is significant ($.001 < p < .01$).

The relationship between dT/dt Min and D.T. for the same contractions as in Fig. 3,*A* is shown in Fig. 3,*B*. Again an excellent correlation is found ($r = .990$), but in this relationship the slope of the regression of dT/dt Min and D.T. is not significantly different from the line of identity ($p > .10$), showing an almost exactly parallel increase in both parameters when the muscle length is increased. A similar parallelism between the T.I.T. and D.T. is shown in Fig. 3,*C*. A striking correlation is again evident ($r = .996$), with

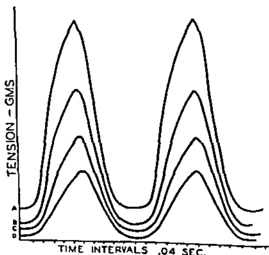


Fig. 4. Direct tracings of the original recordings of the isometric tension curves are superimposed to show the constancy of the time course of tension and the duration of contraction as the segment length is decreased stepwise (*from above downward*). The relative degree of stretch at the various lengths can be inferred from the "passive" (diastolic) tension. The actual segment lengths were: *A*, 4.0 cm.; *B*, 3.8 cm.; *C*, 3.6 cm.; *D*, 3.4 cm. Minimal isometric length = 3.2 cm. The length of *A* was, therefore, 125 per cent of the minimal isometric length.

the stretch on the sample of muscle was barely detectable. The same author reported that if the strain-gauge arch was fixed to the right ventricle, constriction of the pulmonary artery could result in considerable change in the contractile force recorded by the arch. He further demonstrated that such influences could be minimized by increasing the stretch on the segment of muscle attached to the arch. Additional evidence that adjacent muscle did not appreciably alter the measurements of this study was gained through experiments in which the size of the heart was suddenly decreased by incising the ventricle. Almost no changes were noted in any of the aspects of tension of the segment in the first several beats after the incision had been made, although ventricular pressure immediately dropped to near zero.

Results

1. Relationship of contraction to fiber length. When the length of the myocardial sample was increased stepwise by approximately 20 per cent from a length at which any passive or end-diastolic tension could just be detected, a strikingly parallel and almost linear increase in the developed tension, the rate of tension development and relaxation, and the time integral of developed tension occurred. Increases in length of greater than 25 per cent were not studied because pilot experiments showed that such extreme degrees of stretch resulted in changes in the preparation so that, when the stretch series was repeated, a diminution in the passive tension at any length was found. Similarly, a diminution in the amplitude of each of the other parameters at any given fiber length was noted. The cause of such changes is not clear. Possible explanations considered were: (1) cutting of muscle fibers by the suture; (2) tearing of muscle fibers; (3) a type of stress relaxation; (4) disruption of the contractile mechanism; (5) various combinations of these factors. Similar changes in isolated skeletal muscle preparations have been noted by other investigators and attributed to irreversible stretching of series elastic elements.[11] If the stretch did not exceed approximately 25 per cent, these changes were minimized,

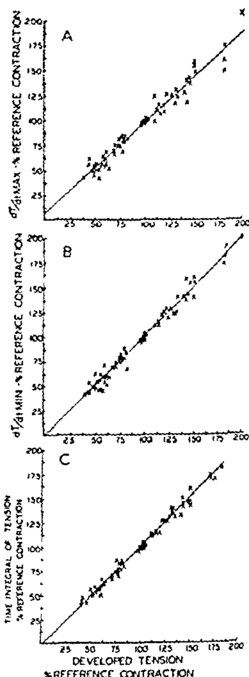


Fig. 3. The proportionality of the increase of each of the measured aspects of active tension in all dogs as fiber length alone is altered is shown. All values are expressed as a percentage of a reference contraction selected for each dog from the middle length of the stretch series. Thus, by definition the percentage values at x = 100, y = 100 are nearly identical. This procedure tends to establish the point of rotation of the regression but does not force a correlation of the remaining points nor otherwise influence the slope of the regression. An excellent correlation for all three relationships is seen with the calculated regression lines.

2. Relationship between contraction parameters and fiber length with altered contractility. Many previous studies have established that the maximum tension produced by the myocardium contracting isometrically is increased at any given length of the muscle by epinephrine, digitalis, calcium, and other agents which have a positive inotropic action. Opposite effects have been demonstrated for such drugs as chloroform, quinidine, and potassium salts, which depress myocardial contractility. In the present experiments, when the contractility of the myocardium was increased by infusions of epinephrine, with the heart rate kept constant by electrical pacing, D.T., dT dt Max, and dT/dt Min were regularly increased at any given fiber length. However, in only 5 of the 9 dogs in which a myocardial response to epinephrine was observed was the time integral increased at a given fiber length. In the other 4 animals it was either unaltered or slightly decreased. Fig. 5 shows these changes in a single experiment in which all contraction parameters were increased by epinephrine.

This variable response of T.I.T. could not be related to the rate of pacing, which was similar in both groups, but apparently could be related, *at least in part, to the* magnitude of the inotropic changes induced; the greater the increase in D.T. and dT/dt Max, the more likely was the integral to be increased. This trend is apparent in Fig. 6. This variation could not readily be related to the duration of systole, which was decreased appreciably in all instances by the administration of epinephrine. It is apparent that the time integral of tension is the resultant of both the intensity of contraction and the duration of systole, which tend to be influenced in opposite directions by epinephrine. The extent of such changes is evidently not necessarily of the same magnitude.

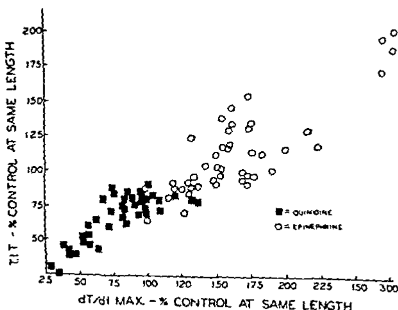


Fig 6. The relationship between T.I.T and dT/dt Max for all dogs during the epinephrine and quinidine experiments is displayed. The values of both variables are expressed as a percentage of the same function at the same segment length during the control experiment on the same dog This allows the effect of the fiber length to be discounted A value of more than 100 per cent of either variable would indicate an increase in contractility if it were used as the index to such alterations. When the epinephrine effect was least, the integral of tension was frequently decreased as compared to the control, although in no instance was dT/dt Max decreased below its control value. Similarly, when the quinidine effect was minimal, dT/dt Max was sometimes increased, although T.I.T. was never increased by quinidine.

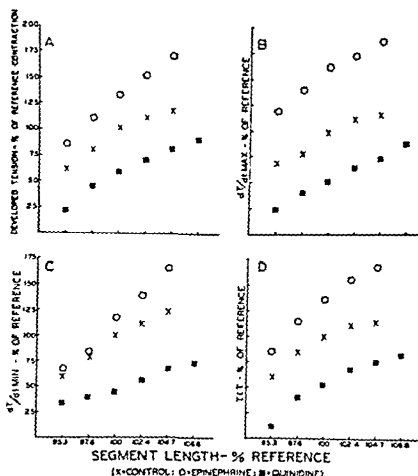


Fig. 5. These graphs are from a single dog. Each of the functions of isometric tension were increased by epinephrine and decreased by quinidine at any given fiber length, forming a family of "ventricular function" curves. These findings were typical of those experiments in which the effects of the drugs were marked.

the slope of the regression of T.I.T. on D.T. not significantly different from identity ($.05 < p < .10$).

To summarize, when the muscle length is increased over a considerable physiologic range, and heart rate and contractility remain constant, the percentage increments of the maximum rate of decline in tension, the time integral of developed tension, and the maximum tension that is developed during contraction are all identical. The percentage increment of the maximum rate of tension development with increasing muscle length is proportional to the other variables but not identical, the proportionality constant being significantly less than one.

The total *duration of contraction* under the isometric conditions of these experiments was not measurably altered by variations in fiber length. This fact, graphically portrayed in Fig. 4, was confirmed by direct measurement in all experiments. Similarly, the time to peak tension was not changed when fiber length alone was altered. The constancy of the duration of all phases of contraction is suggested by the fact that changes in the time integral of tension and the maximum developed tension were virtually identical (Fig. 3,*C*). These findings are not new[5] but are restated because of a common belief that the duration of contraction is a function of fiber length. This is not to imply that the duration of ejection is unrelated to fiber length. The duration of contraction at a constant load is, however, independent of the stretch on the muscle.

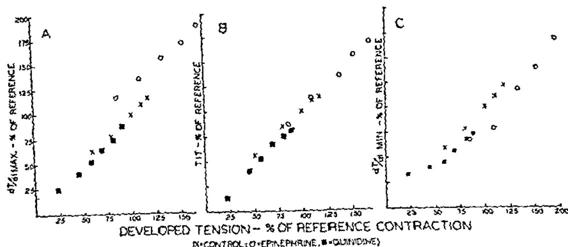


Fig. 7. The relationship between D.T. and its rate functions for a single dog as both stretch and contractility are varied is shown. The variations of the functions during a given state of contractility are the result of a systematic variation in segment length.

tremely great. This is in part due to the changing length of the muscle, which results in a continuously changing position on the active portion of the length tension curve, even during a single contraction,[11] and in part to the force-velocity phenomenon of muscular contraction.[12] Since the tension exerted by a contracting muscle will vary inversely with the velocity of shortening, no direct or indirect measurement of either tension or shortening could be expected to vary predictably with fiber length unless this effect be completely accounted for.[13]

In an isometric contraction these factors relative to changing gross length are minimized, and analysis thereby simplified to some extent. It is appreciated that shortening of some part of the contractile mechanism is necessary for tension to develop, and that an isometric contraction is also a complex function. The degree of shortening, however, is so slight as compared to isotonic conditions as to diminish the attendant complexities proportionately.[12]

Frank, in his classic investigations on isovolumetric contraction in the turtle heart, noted that an increase in initial or pre-excitation tension would be accompanied by an increase in the amplitude of contraction, rate of tension development, and time integral of tension.[3] He did not, however, report a systematic analysis of the quantitative aspects of these variables nor of their interrelationships when stretch or contractility was altered. Numerous other investigators have studied the relationship between fiber length and the tension of cardiac muscle during both active and passive states to define the length-tension relationship of cardiac muscles under a variety of conditions. The present studies were intended to examine directly the relationship of the developed tension, its time derivative, and integral to the fiber length, under various states of myocardial contractility. To our knowledge, a systematic analysis of these relationships under such conditions has not been reported previously. The results show clearly that the effect of an increased fiber length in a segment of cardiac muscle contracting isometrically is to increase the rate of tension development and relaxation in proportion to the increase in length, without altering the duration of contraction. Thus, an increased fiber length in cardiac muscle contracting isometrically results in predictable increases in the rate of tension development, the rate of relaxation, the developed tension, and the time integral of tension. It is apparent from the foregoing that, if the inotropic condition is unchanged, the measurement of a change of dT/dt Max at any new fiber length allows a confident prediction of the change in D.T., dT/dt Min, and T.I.T. which results from the altered length.

The effect of quinidine was to decrease in every experiment the D.T., dT/dt Min, and T.I.T. at any given fiber length (Fig. 5). In most experiments, dT/dt Max was decreased also, but to a lesser extent than was D.T. or T.I.T. In two experiments, dT/dt Max was increased at a given fiber length when T.I.T. was decreased, as shown in Fig. 6. It is evident that such a response was seen when the severity of the depression was least. The duration of systole was *not predictably altered by* quinidine. In some instances, the duration of systole was decreased significantly, whereas in others it was unaltered or increased slightly. These differences could conceivably be a result of the variable stimulation received by the heart from the sympathetic nervous system, since the arterial pressure was always decreased, but to different levels, by the administration of quinidine. No attempt was made *to maintain blood pressure constant or to* block the action of the sympathetic nerves.

3. Interrelationships between contraction parameters when contractility is altered. As already demonstrated, when length alone is altered, there is a proportional increase in D.T., dT/dt Max., dT/dt Min., and T.I.T. When contractility is increased by the infusion of epinephrine, all of these functions are increased at any given segment length, except T.I.T., which may vary *in either direction. However,* dT/dt Max is increased relatively more than are any of the other variables. Quinidine resulted in a proportionate decrease in D.T., dT/dt Max, dT/dt Min, so that their interrelationship was not altered, but the T.I.T. was decreased more than were the other contraction parameters. These relationships are depicted in Fig. 7 *for a single dog, and in Fig. 8 utilizing all* data from the 10 dogs. Fig. 8,*A* shows the relationship between D.T. and dT/dt Max. That the rate of tension development is increased more than the developed tension by the influence of epinephrine is shown by the significantly steeper slope of the regression of dT/dt Max on D.T. as compared to the control regression ($p < .001$). *This relationship was not altered by quinidine,* since the difference in slope of regression between the control and quinidine experiment is not significant ($p > .10$).

Fig. 8,*B* shows the relationship between the rate of relaxation (dT/dt Min) and the developed tension. Analysis of the effects of either quinidine or epinephrine failed to reveal any significant variation from the control relationship. This finding was of interest because of the differences noted between dT/dt Max and D.T. during the same experiments. It follows that dT/dt Max was increased more than dT/dt Min by epinephrine, but decreased *to the same extent as dT/dt Min by quinidine.*

Fig. 8,*C* illustrates the effects of epinephrine on the relationship between D.T. and T.I.T. There was a slight, but highly significantly greater increase in D.T. than T.I.T. when epinephrine was given ($p > .01$). Almost exactly similar changes were seen in the quinidine experiments. It is apparent, therefore, that this relationship does not vary directionally *according to the state of myocardial contractility,* nor does the relationship between dT/dt Max and T.I.T., as may be seen in Fig. 6. The ratio dT/dt Max/T.I.T. could be increased by either quinidine or epinephrine.

Discussion

The fact that contraction of cardiac muscle is quantitatively affected by the degree of stretch upon the muscle at the *time of excitation* has been established since the experiments of Frank in 1895,[5] and Starling in 1914.[6] Exactly what aspects of contraction are affected and how they are altered is by no means clear, as has recently been pointed out by Katz.[18] In fact, a considerable controversy relative to this matter still exists despite an extraordinary number of studies of the relationship between fiber stretch and contraction. Much of this confusion stems from the fact that fiber stretch is only one of several important modulating influences upon the contraction of the myocardium. These include the "physiologic fitness" or contractility of the muscle, the resistance to shortening, and the heart rate as well as stretch. If the effect of any one of these *influences is to* be examined discretely, the others must be controlled or taken into account. In an ejecting or shortening beat, the complexities of analysis are ex-

with an elastic component. The shortening of this contractile element transfers energy from itself to the elastic, thereby extending it and producing tension. The rate of internal shortening should be reflected in the rate of tension development, the exact relationship between the two being determined by the properties of the series elasticity. According to the force-velocity relationship, one would expect that the maximal velocity of shortening of the contractile element would be greatest at the very onset of contraction, when the stretch of the series elasticity (load on the muscle) is least. Therefore, dT/dt Max should also occur at the very onset of contraction, barring very alinear properties of the series elastic component. However, as seen in Fig. 1, dT/dt Max is achieved only after 30 to 90 milliseconds have elapsed after the first visible increase in tension This time interval was not altered appreciably by increasing stretch nor did it vary predictably with heart rate or with epinephrine or quinidine. The reasons for the delay in the time of dT/dt Max cannot be ascertained from the present experiments. It is probable, however, that a major part of this delay is a result of asynchronization of the contracting units. Abbott and Ritchie[15] have shown a gross diminution in the interval between the end of the latent period and the time of maximal rate of shortening of skeletal muscle (frog) when the muscle was simultaneously stimulated at many points along its length, as compared to a single stimulus at one end. However, their studies revealed only slight differences in the maximal velocity of shortening, once attained. In the present experiments a definite increase in this time interval (10 to 30 milliseconds) was noted in most but not all the experiments when the initiation of the heartbeat was transferred from the normal pacemaker conduction system to the pacing electrodes. Simultaneously, a slight decrease in the developed tension and all its functions was noted, as well as a decline in aortic pressure. It seems likely that such changes reflect a greater degree of asynchronism of the contractile units of the ventricle.

These observations lead one to certain speculations in regard to the measure of contractility. This elusive property of the myocardium is frequently discussed, assayed, and changed, but very rarely defined in quantitative terms. More frequently, it is described qualitatively and assayed by inference For the purpose of this discussion, contractility will be taken as an expression which describes the functional state of the contractile mechanism of the myocardium relative to its chemical composition and background. It is assumed to be independent of the stretch on the muscle and the resistance to shortening. Recently, two methods of relatively quantitative analysis have been widely employed. One of these relates the stroke work of the ventricle to some index of fiber stretch as the volume of the ventricle is systematically altered. Changes in the relationship between these variables are ascribed to changes in contractility. As already mentioned, however, stroke work is a complex function of myocardial contraction and extracardiac factors. A confident interpretation of even the direction of changes in myocardial contractility is theoretically impossible unless the resistance to shortening of the muscle is controlled or taken into account Since the resistance to shortening is also a complex function in the intact ventricle, being dependent upon the pressure, the size, and the geometry of the ventricle, present knowledge does not allow a critical analysis of the validity of the studies of myocardial contractility that have been published using these parameters. This is not to imply that extremely useful knowledge as to the effect of various interventions on the circulation is not gained by such studies. They would appear, however, to give a more reliable idea as to the *effectiveness* of the heart at a given filling pressure than to the functional state of the myocardium.

The other widely used approach to the assay of contractility is the measurement of the maximal isometric tension developed by contraction of the myocardium considered in relation to the stretch on the muscle. This measurement has been the basis for many pharmacologic studies utilizing an isolated muscle preparation, and for in vivo studies using the Walton-Brodie strain-gauge arch, Recently, Katz[3] and others have obtained the same basic

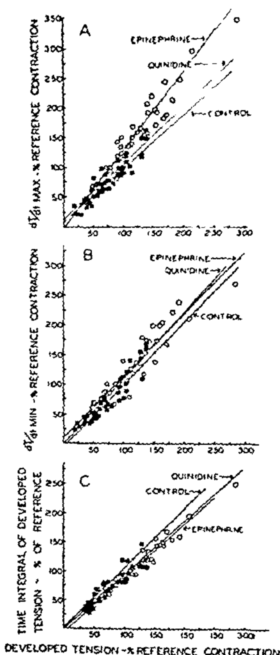


Fig. 8. The interrelationship between D.T. and its functions for all dogs is displayed. The control values are not replotted in this graph (see Fig. 3) but are represented by the calculated regression line marked *control*. The difference in the slope of the regression of dT/dt Max on D.T. for the epinephrine measurements as compared to the control regression is highly significant, indicating a disproportionate increase in dT/dt Max by epinephrine. In C, the slopes of both the epinephrine and quinidine regressions are significantly different from the controls but are not significantly different from each other.

Obviously, any one of these measurements allows such a prediction of the others. However, the fact that dT/dt Max is attained very quickly after the onset of contraction makes this measurement of particular interest. In an ordinary heartbeat, dT/dt Max, as reflected by the time derivative of pressure, is attained prior to the onset of ejection and is thus independent of the resistance to shortening that subsequently influences the maximal tension and the time integral of tension.[8] This independence has been confirmed experimentally by Hendry and Blakey,[11] who showed that the maximal rate of rise in pressure was not different in successive heartbeats when the aorta was ligated in the intervening diastole.

The experiments in which contractility was increased by epinephrine, however, show that the interrelationships between these aspects of contraction are not fixed. The disproportionately greater increase in the rate of tension development than in the developed tension, and the failure of the integral to increase in some experiments in which the developed tension and rate of tension development increased, is consistent with the observed decrease in the duration of contraction. This effect of epinephrine on the duration of contraction has been well documented by many previous investigators. To summarize, the administration of epinephrine results in an increase in the rate of tension development and a decrease in the duration of contraction. The changes in the developed tension and the integral of tension are the resultants of these changes, which are not necessarily proportional, even when the heart rate is controlled. The duration of systole tended to be shortened relatively less than the rate of development was increased, leading to an increase in the maximal tension that was developed per beat.

Since the force-velocity relationship of muscle is one of its most significant mechanical characteristics, it is of interest to consider these data in relation to this aspect of contraction. Even though the gross length of muscle was kept very nearly constant, it is evident that some shortening of the contractile elements occurred. The unit of contraction is generally conceived to be a shortening unit in series

As of the moment, any answer to these questions must necessarily be entirely arbitrary and strongly dependent upon the viewpoint and objectives of the individual worker. It seems desirable, therefore, to consider any agent or intervention in terms of not one but several quantitative aspects of contraction, such as those utilized in this study. The parameters should be independent of extracardiac factors at the moment of measurement. The value of each of these measurements should continuously be enhanced as additional knowledge is gained relative to their mechanochemical significance. Even without such knowledge these multiple measurements may enable one to appreciate differences in various agents affecting contraction that might escape notice if only one of these measurements were made. The differences between the effects of increasing stretch and of the infusion of epinephrine are an illustration of this possibility. Such an analysis suggests that the depression of contraction by quinidine is not simply the reverse of the enhancement of contraction by epinephrine. Rather, the results of this study suggest that a qualitatively different mechanism may be involved. Similarly, differences in various inotropic agents might become apparent if studied in such a manner.

The results of this study support in major part the findings previously reported.[7] At any given state of contractility, dT/dt Max was shown to be a linear function of fiber length. Also, at any given fiber length, dT/dt Max was increased by epinephrine and decreased by definitely depressant doses of quinidine. However, our hypothesis that dT/dt Max would maintain a fixed relationship to the developed tension of an isometric contraction was shown to be an oversimplification. As shown in Fig. 8,*A*, the over-all correlation between D.T. and dT/dt Max was excellent as both fiber length and contractility were altered. Indeed, it is far better than that found between the maximal rate of rise in pressure and the calculated maximal tension of the same beat in the left ventricle in our previous experiments. However, as already discussed, significant differences in this relationship were obtained by the epinephrine and quinidine interventions. The same reservations mentioned above relative to the use of any single aspect of contraction as an index to the still quantitatively undefined property of cardiac contractility apply to the use of the maximal rate of pressure development, however corrected for heart size, or fiber stretch, as to the use of dT/dt Max in a muscle strip. Until more knowledge is gained, its use, and use of the developed tension as an index to contractility, must be qualified by the considerations discussed.

Summary

The developed tension, the time derivative of tension, and the time integral of tension of segments of cardiac muscle contracting isometrically under conditions of altered length and contractility have been studied. The result of an increase in fiber length when heart rate and contractility are constant is to increase the rate of tension development and relaxation without altering the duration of any phase of contraction. The maximal developed tension and the integral of tension are, therefore, increased in proportion to the rate of development and relaxation of tension. The infusion of epinephrine resulted in an increase in the rate of tension development and a decrease in the duration of contraction. Consequently, the developed tension and the integral of tension were increased to a lesser extent than was the maximal rate of tension development. The effect of severely depressant dosages of quinidine was to decrease the rate of tension development without a predictable alteration in the duration of contraction, resulting in a proportionate decrease in the developed tension and the integral of tension. Lesser degrees of depression were sometimes accompanied by a slight increase in the rate of tension development, although the developed tension and the integral were frequently decreased under those conditions. There is no necessary reason apparent why any one of the time functions of isometric tension should be more directly related to myocardial contractility than the others. The variable responses to inotropic interventions of these functions, therefore, poses a number of questions as to the definition and measurement of the contractility of the myocardium.

measurements from isovolumetric contractions of the entire ventricle. Contractility has been equated to the maximal tension that is developed at a given or fixed end-diastolic fiber length. However, there is no necessary reason from previously available evidence why this aspect of contraction should be more appropriate for the estimation of contractility than would some other reflection of contraction, such as the rate of tension development, the rate of relaxation, or the integral of tension. As has been shown in these studies, these contraction parameters may respond differently both quantitatively and directionally to a change in the inotropic state. In all of the experiments, dT/dt Max, dT/dt Min, and D.T. increased when contractility was "increased" in response to epinephrine. The magnitude of the changes, however, were quite different; dT/dt Max almost invariably showed a greater percentage increase than did D.T., whereas dT/dt Min closely paralleled D.T. Similar discrepancies between these variables may be even more apparent when the frequency of contraction or heart rate is altered, as has been previously pointed out.[16] In both of these conditions (epinephrine and heart rate) the variation between D.T. and dT/dt Max would seem to be a reflection of the altered duration of contraction. This possibility is further supported by the observations reported here in relation to the changes caused by quinidine. This agent reduced dT/dt Max and D.T. in almost exactly the same proportion and did not significantly alter the duration of contraction. Since these parameters do not necessarily vary in parallel to inotropic interventions, it is evident that they do not both measure the same thing. Since there is no general agreement as to what constitutes or determines contractility, we doubt that it is possible at present to define or assay this quantity by any simple or single measurement. Thus, one intervention might increase the rate of tension development but decrease the duration of contraction such that the maximal developed tension would not be altered. This type of response is characteristic of that seen when the heart rate is increased at certain levels. Another intervention might not change the rate of tension development but would increase the duration of contraction so that the maximal amplitude of contraction would be increased. We have observed this general reaction in the first or second beat after an abrupt decrease in the electrical pacing frequency of a controlled-rate heart.[16] It is possible that the rate of tension development reflects the rate of chemical reaction, and that the duration of contraction is limited by the amount of substrate that is present.[11] In this event the maximal developed tension would reflect the total substrate utilization of the contraction. This possibility is suggested by the recent work of Lendrum and associates.[17] The response to an increased heart rate, as noted above, could be considered as an increase in contractility if the rate of energy utilization (or chemical reaction) be taken as the criterion for contractility, even though the total energy of the contraction were not altered. Conversely, the second type of reaction described above could be taken to represent an increased contractility if the total energy of the beat be used as the criterion. Other agents, such as epinephrine, would apparently increase both the rate of chemical reaction and the total energy produced, according to this reasoning.

We would emphasize that presently available evidence is conflicting and does not allow a precise identification of the relationship between the mechanics of cardiac muscle contracting isometrically and its energy utilization, although there is much evidence that such a relationship may, in fact, exist. For example, there is evidence that the time integral of tension rather than the maximal tension reflects the total substrate utilization.[3,18] If this is true, then the developed tension would be proportional to the rate of chemical reaction, and the derivative of tension would reflect the rate of change in the rate of chemical reaction. In either event, however, the same reasoning relative to the definition and criterion of contractility would apply. Is the rate of chemical reaction the criterion, or is it the total energy liberated? In terms of the heart as a pump, extracardiac factors being equal, is the power or the work the measure of contractility?

Case reports

Endocardial fibroelastosis associated with glycogen tumors of the heart and tuberose sclerosis

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Endocardial fibroelastosis occurs usually as an isolated defect of the left side of the heart. An occasional association with generalized glycogen storage disease[1] and with glycogen tumors of the heart[2] is of interest since, although the combination may be fortuitous, a causal relationship cannot be excluded. This report describes the unique triad of endocardial fibroelastosis, glycogen tumors of the heart, and tuberose sclerosis.

Case report

The patient was a 10-month-old white male infant who weighed 8 pounds, 11 ounces at birth. There were no siblings, and both parents were young and in good health. During the first few months of life the patient had frequent colds and upper respiratory infections. He was hospitalized at 5 months of age with fever and heart failure Neurological examination was normal. No skin lesions were present

Examination of the chest revealed bilateral basal râles. The cardiac impulse was diffuse, and the left cardiac border was percussed at the anterior axillary line in the sixth intercostal space. The pulmonic second sound was accentuated and snapping in character A blowing, Grade 3/6 systolic murmur was audible over the whole precordium and maximal in the third intercostal space at the left sternal border. The electrocardiogram (Fig 1) showed a heart rate of 150 beats per minute The P-R interval averaged 0 11 second, and the QRS complex, 0 11 second In the precordial leads the T waves were upright in Leads V_1, Rv_3, and Rv_4, biphasic in Leads V_5 and V_6, and inverted in Leads V_2 and V_4 Left axis deviation and left ventricular hypertrophy were diagnosed

The chest x-ray film (Fig. 2) showed a greatly enlarged heart, with marked bulging of the left cardiac border and elevation of the horizontal axis. The barium swallow indicated enlargement of the left atrium and ventricle Subsequent films, taken when the patient was 6, 8, and 9 months of age, showed no significant change in cardiac size or shape.

Cardiac catheterization revealed no abnormal communications between the left and right sides of the heart. Oxygen saturation was normal. The pressures (in millimeters of mercury) were recorded as follows: right atrium, 7/0; right ventricle, 35/0, pulmonary artery, 31-35/13-7. The pressure curve showed no diastolic plateau and was considered to be normal Cineangiocardiography demonstrated a normal right ventricle, with no obstruction to the outflow tract The left atrium and ventricle were greatly enlarged, and considerable regurgitation

Table I. Glycogen content of tissues

Tissue	Grams of hexose/ 100 grams of tissue (wet weight)
Large rhabdomyoma	2 30
Adjacent myocardium	0 21
Diaphragm	0 13
Liver	0.79
Kidney	0 09
Brain (sclerotic cortical nodule)	0 05

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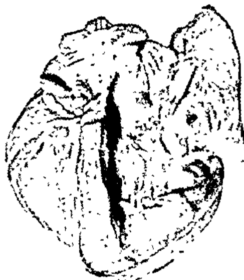


Fig. 3. Right ventricle The bulge of the largest glycogen tumor is seen to the left of the photograph, and the pearly-white cut surface of one of the smaller tumors is also demonstrated

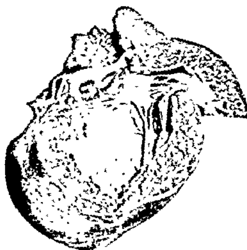


Fig. 4 Left ventricle. Endocardial fibroelastosis The outline of the large anterior rhabdomyoma is also seen.

and Best's carmine and were digested by diastase. No neutral fat was demonstrated. The normal cardiac muscle showed no excess of glycogen granules Several small foci of cells, mainly lymphocytes and a few polymorphonuclear leukocytes, were seen in the myocardium. The endocardium of the left side of the heart was evenly thickened with fibroelastic tissue, the underlying muscle showed no fibrosis. The sinoventricular conduction system appeared to be normal.

Biochemical studies. Glycogen determinations were performed on tissue frozen at the time of the autopsy. The glycogen was precipitated and hydrolyzed by the method of Good, Kramer and Somogyi, as described by Hawk, Oser and Summerson.[3] The hexose was measured by the method of Nelson[4] and Somogyi.[5]

Analyses were performed on tissue from the large tumor mass, a portion of normal left ventricle adjacent to the tumor, a sclerotic nodule of cerebral cortex, and on the diaphragm, liver, and kidney. The results of these determinations appear in Table I.

Discussion

Glycogen tumors of the heart are regarded as developmental anomalies rather than true neoplasms. The nature of these tumors and their relationship to glycogen storage disease and tuberose sclerosis is discussed in detail by Wartman and Hill.[6]

The glycogen-laden nodules in the myocardium rarely exceed 2 cm. in diameter, and progressive enlargement has not been reported. Although one of the tumors in



Fig 5 Photomicrograph of glycogen tumor (hematoxylin and eosin; ×400). The water-clear, glycogen-storing portions of the tumor cells are traversed by spider-like processes of sarcoplasm.

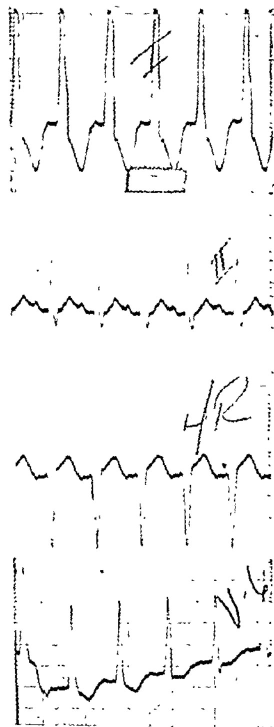


Fig. 1. Electrocardiogram taken when the patient was 5 months old. The tracings indicate marked left ventricular hypertrophy, the P-R interval and QRS complex are equal.

through the mitral valve with incomplete emptying of the left ventricle was observed. The left ventricular wall was much thicker than normal. Endocardial fibroelastosis was the favored diagnosis.

The child responded to treatment with antibiotics and digitalis and was discharged. Subsequently, his condition appeared to be unchanged, until the sudden collapse and death at the age of 10 months.

Pathology. Postmortem examination was performed 12 hours after death. The body was well nourished and weighed 23 pounds. Significant findings were limited to the brain and to the heart.

BRAIN. The brain, which was slightly larger than normal (900 grams), showed gross and microscopic evidence of tuberose sclerosis with numerous cortical and basal-nuclear tubers. Histochemical stains showed no evidence of glycogen storage in the lesions.

HEART. The heart (155 grams) almost filled the chest. A large, globular tumor, 9 cm. in diameter, projected from the surface immediately anterior to the interventricular septum (Fig. 3). Three smaller nodules were embedded in the right ventricular muscle. The masses exhibited the typical fleshy pallor of glycogen tumors.

The endocardium of the left side of the heart was pearly white, smooth, and glistening (Fig. 4). The endocardial thickening, which was maximal beneath the aortic valve, involved the whole of the left ventricle and extended through the mitral valve into the atrium. There were no other anomalies; the coronary arteries and great vessels were normal.

Microscopic examination showed numerous, tiny tumors scattered throughout the myocardium. The histologic appearance of the small and large tumors was similar. There were no distinct capsules, although a little condensed fibrous tissue served to demarcate the nodules from the normal heart muscle. A few, normal cardiac muscle fibers were incorporated in the nodules. The typical tumor cell, ballooned up to 80μ in diameter, contained a large, central nucleus surrounded by a rim of sarcoplasm from which spider-like processes radiated through the abundant clear cytoplasm (Fig. 5). The tumor cells were rich in granules which stained with P.A.S.



Fig. 2. Chest x-ray film taken when the patient was 5 months old shows marked bulging of the left cardiac border, with elevation of the horizontal axis.

The syndrome of post-traumatic pericarditis

A case report

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Pericardial effusion after blunt trauma to the chest has long been recognized. In 1897, Maullin[1] reported on a patient with effusion that he attributed to injury of a coronary artery; however, the description of the fluid and the apparent recovery of the patient suggest that this probably was the first well-described case of "nonspecific pericarditis" after injury to the heart. Goodkind and associates,[2] in a recent report, related this type of effusion to the postmyocardial infarction syndrome of Dressler and first demonstrated the dramatic effect of steroids in post-traumatic pericarditis. More recent reviews of the entire subject by Kissane and Rose[3] and by Tabatznik and Isaacs[4] have brought the relationship to the postpericardiotomy syndrome into focus.

A case report

H. K., a 28-year-old white woman, was brought to MacNeal Memorial Hospital on April 28, 1960. She had just been in an automobile accident and had suffered head injuries, a steering-wheel injury of the chest, and lacerations of both legs. She arrived unconscious and in shock. Examination revealed multiple fractures of the ribs on the right side and evidence of fluid in the right chest cavity. She had multiple lacerations of both knees and contusions about the head. Examination of the heart at this time revealed no abnormalities. An electrocardiogram taken at the time she was admitted to the hospital revealed slight elevation of the S-T segments and early terminal T-wave inversions over the anterior wall. The shock was relieved promptly by blood transfusions, and the patient regained consciousness. Six hundred and fifty cubic centimeters of fresh blood were removed from the right chest cavity, and on subsequent thoracenteses, which were done over the next 3 days, an additional 2 liters of blood were removed from the same side

On May 4, the patient became more dyspneic and had a temperature of 102°F. No friction rub was heard at this time, and the pulse and blood pressure were normal Venous pressure was 160 mm. of saline. The patient then continued with a low-grade fever until May 11, when she again spiked a temperature to 102°F. At this time the white blood cell count was 12,700, with 76 neutrophils, 7 bands, 14 lymphocytes, and 3 monocytes. The patient continued to have a fever of 101° to 102° F , and on May 16, she complained of severe precordial chest pain which was aggravated by breathing, and marked dyspnea on the slightest movement. She was most comfortable sitting up in bed At this time a loud pericardial friction rub was heard for the first time.

A chest x-ray film taken the next day revealed marked enlargement of the cardiac silhouette, and, in addition, there was pulmonary infiltration in the left lower lung field and some pleural fluid on the left, as well as the pathology which was previously present in the right side of the chest. Fluid removed from the left pleural cavity was clear, and cultures were sterile. Tuberculin and histoplasmin skin tests were negative. Thinking that the patient's condition was infectious in origin, we placed her on tetracycline.

On May 21, the white blood cell count was 9,400; hemoglobin was 11.5 Gm. per cent, sedimentation rate 40 mm. per hour, total protein 7.5 Gm. per cent, and A/G ratio 4.0/3.5. The patient had remained febrile despite the antibiotic therapy, and

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the patient under discussion was 9 cm. in diameter, the radiologic studies indicated that no significant increase in the size and shape of the heart had occurred between the fifth and the ninth months.

The anatomic demonstration of several large cardiac tumors raises the question of antemortem diagnosis. Careful review of the x-ray films and cineangiocardiograms showed nothing which could be interpreted as a cardiac tumor. The electrocardiographic tracings tended to confirm the diagnosis of endocardial fibroelastosis. The approximation of the P-R interval to the duration of the QRS complex is of interest since this finding has been reported in glycogen storage disease of the heart.[7]

The presence of glycogen in tumors of cardiac muscle has often been demonstrated by histochemical techniques, only two quantitative studies have been reported, however.[8,9] In the present investigation the glycogen content of the tumor was similar to the values which have been recorded in glycogen storage disease, a finding which may add some support to the theory that glycogen tumors of the heart represent a form of glycogen storage disease.[9,10]

The occasional occurrence of endocardial fibroelastosis with such metabolic disorders as glycogen storage disease, gargoylism,[11,12] and nutritional hypoproteinemia[13,14] has been reported. If glycogen tumors are in any way related to glycogen storage disease, the present case may be regarded as another instance of the association of endocardial fibroelastosis with a metabolic disease.

Summary

Endocardial fibroelastosis, associated with glycogen tumors of the heart and tuberose sclerosis, is described in a 10-month-old boy. The relationship of endocardial fibroelastosis to glycogen storage and other metabolic disorders of the myocardium is discussed.

The authors are greatly indebted to Dr. J. Gerrard Mudd and Dr. James L. Donahoe for their assistance with the preparation of this paper.

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8 weeks was then made without event. The patient had been on steroids a total of 11 weeks.

Discussion

The description by Barnes and Burchell[5] of acute pericarditis simulating acute coronary occlusion first aroused interest in the syndrome of recurrent episodes of nonbacterial pericarditis associated with fever and chest pain. This was thought to be viral in origin, and Carmichael[6] showed a frequent correlation with preceding upper respiratory infections. In 1953, a similar syndrome after mitral commissurotomy was described by Soloff and associates.[7] This was attributed to reactivation of rheumatic fever, but the authors were unable to link the occurrence of the syndrome to any known measurement of rheumatic activity either before or after surgery. Epstein[8] reviewed the evidence for and against a rheumatic etiology of the postcommissurotomy syndrome and concluded that the condition was most likely related to the pericardiotomy and was not of rheumatic etiology. He suggested that an autoimmune mechanism would offer an attractive hypothesis.

In 1955, Dressler[9] described a syndrome of recurrent pericarditis after myocardial infarction and noted that it closely resembled recurrent idiopathic pericarditis. He treated some of these patients with steroids and observed relief of pain, fever, and the signs of pericarditis.[10] By 1959, Dressler,[11] had collected 44 personal cases of this syndrome after myocardial infarction and cautioned against the use of

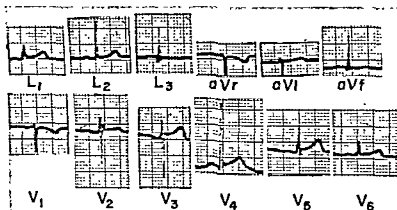


Fig. 5. Electrocardiogram taken on April 28, 1960.

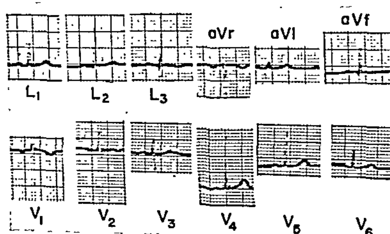


Fig. 6. Electrocardiogram taken on May 24, 1960.

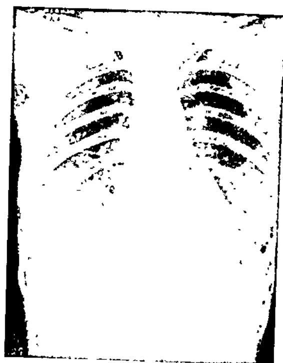


Fig. *1.* Chest x-ray film taken on May 9, 1960

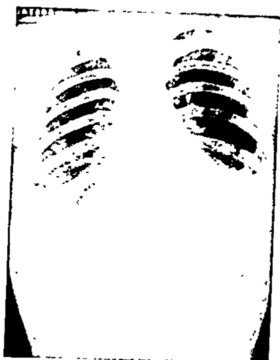


Fig. *3.* Chest x-ray film taken on May 20, 1960.

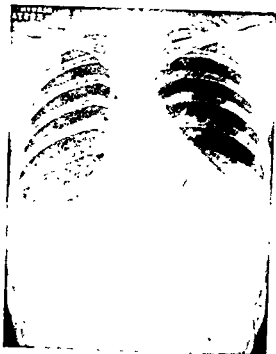


Fig. *2.* Chest x-ray film taken on May 17, 1960.

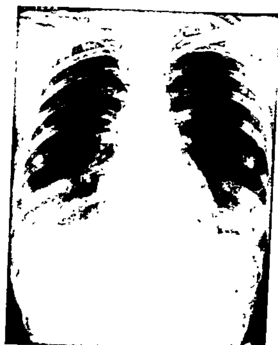


Fig. *4.* Chest x-ray film taken on May 27, 1960.

on May 22, because of the similarities of her condition to the postmyocardial infarction syndrome of Dressler, the patient was placed on 40 mg. of prednisone per day. The next day she became afebrile, the chest pain was less severe, and she felt much improved. On May 27, a chest x-ray film revealed that the pulmonary infiltration had cleared and that the cardiac silhouette had returned to normal size. She continued to improve, except for one episode of sudden return of pain when withdrawal of the steroids was first attempted. Gradual withdrawal of steroids over a period of

Clinical pathological conference

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Ray C. Anderson, M.D.
Larry P. Elliott, M.D.
Kurt Amplatz, M.D.
C. Walton Lillehei, M.D.
Jesse E. Edwards, M.D.
St. Paul, Minn.

DR. SHONE: This patient was examined for the first time at the University of Minnesota Hospitals in December, 1959, when he was 13 years old. He was examined again in 1961. His growth, weight, and developmental pattern were stated to have been normal. However, a routine physical examination when he was 9 months old disclosed a cardiac murmur, and his parents were told that he had a "hole in his heart." There had been no other examination between that time and the time he was referred here.

Direct questioning brought out that the boy's respirations may have been more rapid than normal. It also brought out the fact that he may have had a reduced tolerance to exercise as compared with that of his schoolmates. Digital clubbing had been noted when he was 8 years old. Although he was markedly cyanotic, his parents were reluctant to admit it. They did admit, however, that his color may have been poor since infancy. There was no history of squatting. One episode of hemoptysis occurred 2 years prior to his referral here. It had been associated with "a severe cold." In February, 1961, which was 14 months after his initial referral here, he "passed out in church" and was unconscious for approximately 40 minutes. During this period he was extremely cyanotic and his respirations were rapid.

Our first examination showed a well built, normally developed boy who was extremely cyanotic. The cyanosis was equally severe in the upper and lower limbs. There was moderate digital clubbing that involved fingers and toes. He was dyspneic even on mild exertion. Femoral pulses were easily palpable and were of good volume. Cardiac activity was increased, with regular rhythm. A systolic thrill was palpated in the suprasternal notch. A Grade 3 (on the basis of 1-4), harsh systolic murmur was heard over the left upper parasternal area. It transmitted well to the back. A prominent early systolic ejection click was heard over the same area. It was particularly marked during expiration, when the boy was sitting up. At the pulmonary area, the second cardiac sound (S_2) was split, and both components were softer than normal in intensity. Blood pressure in the right arm was 118 mm. Hg systolic and 80 mm. Hg diastolic. The hemoglobin concentration of the blood was 22.5 Gm. per 100 c.c. of blood. On the basis of studies to be described, surgery was performed in March, 1961.

Dr. Anderson, would you please make some preliminary comments on the diagnostic possibilities suggested by the history and physical findings in this case.

DR. ANDERSON: The boy's medical history is difficult to evaluate because there had

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steroids in patients who were only mildly affected, since he had the impression that therapy tended to facilitate recurrence. He related the syndrome to the postpericardiotomy and idiopathic pericarditis syndromes, and thought that all of these entities may be produced by autoantibodies formed in response to necrotic myocardium.

Just recently, Goodkind[2] related post-traumatic effusion to the syndromes of recurrent pericarditis.

Although pericardial effusion after blunt trauma to the chest had been known since 1897, it was the report by Ehrenhaft and Taber[12] which aroused interest in the probability that the effusion was at least partially due to the presence of blood lipid fractions in the pericardium. This followed shortly upon the report by Overholt and associates[13] that this type of injury can cause not only hemopericardium but can be a cause of constrictive pericarditis. At this time, reports[12-15] were concerned more with the advisability of removal of the pericardium to prevent future pericardial constriction than they were with the etiology of the pericarditis itself. It was left for Goodkind[2] to relate this inflammatory lesion to the postpericardiotomy syndrome, and show the remarkable efficacy of steroid therapy. The case reported herein suggests the possibility that the inflammatory lesion can be controlled by long-term steroid therapy, and perhaps the necessity for pericardiectomy can be averted.

The syndromes of idiopathic pericarditis, postpericardiotomy, postmyocardial infarction, and post-traumatic pericarditis all seem to have the same clinical pattern. It is very possible that they all may have the same etiology. Some investigators have thought that this was reactivation of a virus,[16] but the autoantibodies found in patients with these entities make the speculation by many that these syndromes represent an autoimmune response to myocardial injury a very attractive hypothesis.[17-19]

Summary

A case of pericarditis after blunt trauma to the chest is described. Its relationship to the postmyocardial infarction syndrome of Dressler is discussed and the prompt response to steroid therapy is emphasized.

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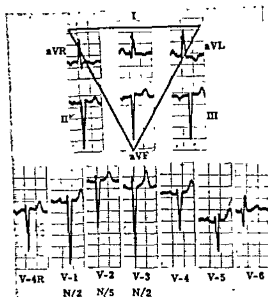


Fig. *1.* The electrocardiogram.

pulmonary venous blood, demonstrating a large right-to-left shunt at the atrial level. These data indicate right-sided obstruction, either at the tricuspid valve or beyond. The low pulmonary venous wedge pressure indicates a normal pulmonary arterial pressure.

One can conclude that there is normal pulmonary arterial pressure, with some type of obstructive lesion between the right atrium and the pulmonary artery. One must consider tricuspid atresia, hypoplastic right ventricle, or pulmonary stenosis, either as single or combined defects. The significant increase in right atrial pressure between the two studies parallels the progressive deterioration in the patient's general condition.

DR. SHONE: Dr. Amplatz, would you comment on the roentgenographic findings.

DR. AMPLATZ: The thoracic roentgenograms revealed only slight cardiomegaly on the posteroanterior film (Fig. 2, *left*). The lateral view (Fig. 2, *right*) suggests that there is some right ventricular enlargement, in that the cardiac border is contiguous with the sternum over a wide area. There is no evidence of any left atrial enlargement. The aorta is prominent, and the aortic arch lies on the left. The pulmonary vasculature is at the upper limits of normal. There is slight prominence of the left pulmonary artery, which suggests the possibility of pulmonary valvular stenosis.

The venous angiocardiogram resulted in a study of poor quality. One can, however, identify a right-to-left shunt at the atrial level (Fig. 3). There is simultaneous visualization of the right and left ventricles, but it is not possible to determine whether the right ventricle fills from the right atrium or through the left ventricle. The right ventricle is of near-normal size, and some infundibular pulmonary stenosis may be present. The great vessels are normally interrelated. The aorta is relatively large.

Table I. *Catheterization data obtained in July, 1960*

Site	*Pressure (mm. Hg)*	*Oxygen content (vol. %)*	*Oxygen saturation (per cent)*	
			Van Slyke	*Oximetry*
Right atrium	13/6(M9)			53
Inferior vena cava				60
Superior vena cava		14 4	50	51
Brachial artery		18 0	62	63

Oxygen capacity: 29.1 volumes per 100 c.c. M: Mean pressure

Table II. *Catheterization data obtained in March, 1961*

Site	*Pressure (mm. Hg)*	*Oxygen content (vol. %)*	*Oxygen saturation (% by oximetry)*
Superior vena cava			39
Right atrium			<30
Inferior vena cava			<30
Pulmonary vein	16/10	26 9	93*
Pulmonary vein (wedge)	14/12		
Left atrium	25/14 (M15)		46
Right atrium	25/10 (*a* wave 25)		

*Oxygen saturation by the Van Slyke method = 93 per cent.
Oxygen capacity: 28 9 volumes per 100 c.c.

been no medical examination from the time of infancy until he was 13 years old. In addition, the observations of his parents apparently were unreliable. It is known that he had a cardiac murmur when he was 9 months old, but the exact time of appearance of cyanosis is not known. Apparently, dyspnea and intolerance to exercise always had been present, although the parents minimized this. Presumably, no squatting had been observed. This makes it unlikely that the lesion is the tetralogy of Fallot. There was a systolic thrill in the suprasternal notch, and a coarse systolic murmur along the upper left sternal border, together with a systolic ejection click that was more prominent when he was sitting up.

These findings suggest a valvular pulmonary stenosis with a large main pulmonary artery. The splitting of the second cardiac sound, together with a soft pulmonic component, indicates a valvular pulmonic stenosis, and it suggests that the ventricular septum is intact. One is led to conclude that the cyanosis is produced by a right-to-left shunt at the atrial level, the diagnosis being valvular pulmonary stenosis with interatrial communication. I suspect that the roentgenograms and electrocardiograms will confirm this diagnosis.

DR. SHONE: Perhaps you would comment on the electrocardiogram, Dr. Elliott.

DR. ELLIOTT: The electrocardiogram (Fig. 1) has unusual features, particularly since the history and physical findings discussed by Dr. Anderson suggest pulmonary stenosis with an interatrial communication. When the clinical profile in a patient is characterized fundamentally, on the one hand, by cyanosis and, on the other, by electrocardiographic features which show left axis deviation and a markedly posteriorly displaced QRS loop in the horizontal plane, represented by stereotype rS complexes across the precordial leads, the most likely diagnosis is cor triloculare biatriatum or single ventricle with obstruction to pulmonary flow.

Of course, electrocardiographic features observed in the frontal plane also may suggest a spectrum of defects of the A-V commune or endocardial cushion types. Conditions characterized fundamentally by cyanosis associated with a ventricular septal defect of the persistent common atrioventricular canal type, or by an atrial septal defect of the so-called ostium primum type, include origin of both great vessels from the right ventricle with pulmonary stenosis, complete transposition of the great vessels, tetralogy of Fallot, and complicated malformations in the syndrome of agenesis of the spleen. The electrocardiographic features not characteristic of A-V commune defects in this patient are the deep S waves across the entire precordium from Lead V_{4R} to Lead V_6.

On occasion, severe pulmonary stenosis with an intact ventricular septum may result in marked posterior displacement of the QRS forces in the horizontal plane, represented by deep S waves in Lead V_1 and Lead V_6. In these instances, however, the QRS loop is clockwise in direction and is orientated to the right, so that the complexes in precordial Lead V_{4R} are represented by tall R waves. In addition, the mean manifest electrical axis in patients with severe pulmonary stenosis should be deviated to the right. The P-wave morphology would be expected to indicate right atrial enlargement. The presence of a q wave in Lead V_{4R} suggests the possibility of some form of congenital corrected transposition, but it may indicate marked elevation of right ventricular pressure.

I would suggest that, on the basis of the electrocardiographic findings, there is some form of common ventricle with obstruction to pulmonary flow.

DR. SHONE: We are planning to have the entire roentgenographic and angiocardiographic data discussed later as a unit. We shall ask Dr. Anderson to discuss the catheterization data now.

DR. ANDERSON: The data of the catheterization on the right side are of limited help (Tables I and II). The right ventricle was not entered on either of two occasions, a fact which favors a diagnosis of tricuspid atresia. It is hazardous, however, to form conclusions on the basis of negative findings.

The right atrial pressure was elevated on both occasions, with large *a* waves seen in the second study. The left atrial blood was markedly desaturated (Table II), in contrast to the normal saturation of the

DR. LILLEHEI: The preoperative diagnosis was tricuspid atresia with a significant reduction in pulmonary blood flow. It was thought that a subclavian-pulmonary artery end-to-side shunt would offer palliation by increasing pulmonary blood flow at only a moderate risk, despite the very poor general condition of the patient.

Using a Teflon graft, an end-to-side anastomosis between the right subclavian and right pulmonary arteries was performed. Upon release of the clamp there was an excellent anastomotic thrill. The anastomosis could have been made without the use of the prosthetic graft by utilizing the full length of the subclavian artery to the very apex of the thoracic cavity. However, this would have made the diameter of the resulting shunt rather small. The pericardium was not opened for exploration.

The patient appeared to be convalescing satisfactorily until 30 hours after the operation, when, rather suddenly, his pulse became irregular and very slow and the blood pressure became unobtainable. Immediate external cardiac massage and other resuscitative measures were started. There were some temporary but short-lived benefits. The patient died about an hour after the initial setback.

DR. SHONE: Dr. Edwards, will you please describe the pathologic findings.

DR. EDWARDS: The left ventricular cavity was moderately enlarged and its wall was hypertrophied. There was a small ventricular septal defect, which measured 9 mm. in diameter, anterior to the posteromedial commissure of the mitral valve in the angle between this area and the muscular and membranous portions of the ventricular septum (Fig. 5, *upper*). The aortic and mitral valves were not remarkable except for small fibrous vegetations attached to the ventricular aspect of the aortic leaflets.

From within the right ventricle the ventricular septal defect was seen to enter below the crista supraventricularis and above the papillary muscle of the conus (Fig. 5, *lower*). The anterior wall of the right ventricle opposite the ventricular septal defect showed a patch of gray fibrous endocardial thickening (*end of probe*). This was interpreted as a jet lesion secondary to the effect of the shunt through the ventricular septal defect from the left ventricle to the right ventricle. Although the right ventricular wall was hypertrophied,

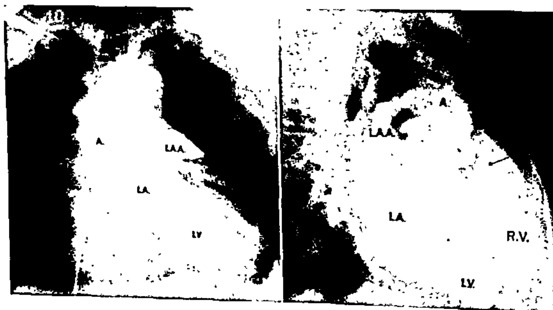


Fig. 4. Selective angiocardiogram made with the catheter in the left atrium. *Left:* Posteroanterior view. *Right:* Lateral view. *L.A.A.:* Left atrial appendage. *A:* Ascending aorta. *L.A.:* Left atrium. *L.V.:* Left ventricle. *R.V.:* Right ventricle. *R.C.:* Right coronary artery.



Fig. 2. Roentgenograms of the thorax. *Left*: Posteroanterior view. *Right*: Lateral view.

Reviewing the films which were obtained by selective angiocardiography from the left atrium, one sees that the left atrial appendage is filled initially (Fig. 4, *left*). After this, there is demonstration of the left atrium proper, and opacification of a fairly large left ventricle. The aorta is densely opacified and is in normal position. The right ventricle opacifies apparently through a ventricular septal defect (Fig. 4, *right*). The right ventricular cavity is of moderate size, and its outflow tract is visualized.



Fig. 3. Venous angiocardiogram, lateral view. *A*: Ascending aorta. *R.V.*: Right ventricle. *R.A.*: Right atrium. *L.A.*: Left atrium.

In view of the catheterization data, these roentgenographic and angiocardiographic findings were thought to be consistent with tricuspid stenosis or tricuspid atresia associated with a ventricular septal defect and pulmonary stenosis.

DR. SHONE: Clinically, this patient was considered to have pulmonary stenosis, with a right-to-left shunt at the atrial level. The subsequent catheterization and angiocardiographic studies were recognized as being of limited value. However, during the selective angiocardiography the passage of opaque material from the left atrium to the left ventricle to the right ventricle and the pulmonary artery was regarded as being most compatible with a diagnosis of tricuspid atresia associated with a ventricular septal defect. This, together with identification of the right-to-left shunt at the atrial level during venous angiocardiography and, further, electrocardiographic evidence of left axis deviation and left ventricular preponderance, led the attending physician to a diagnosis of tricuspid atresia with interatrial communication, ventricular septal defect, and pulmonary stenosis. The patient was referred to the surgical staff for treatment.

Dr. Lillehei, would you describe the operative procedure.

Under ordinary circumstances the degree of pulmonary valvular stenosis present in this patient would direct a shunt through a ventricular septal defect in a right-to-left direction, rather than in a left-to-right one. The tricuspid malformations, however, probably underlie the basis for the peculiarities which are interpreted as having occurred. With coexistent tricuspid insufficiency, the right ventricle would have an outlet additional to that of the pulmonary valve. It would be expected, therefore, that the systolic pressure in the right ventricle would not have risen as high as it would have if the tricuspid valve had been competent.

Evidence for a right-to-left shunt must be sought to explain the cyanosis in this patient. The appearance of the atrial septum offers ample explanation for a right-to-left shunt at the atrial level. This is supported by catheterization and angiocardiographic data.

The shunts in this patient are most unusual in that each of the four cardiac chambers participated (Fig. 7). In the usual instances wherein cardiac chambers participate in a shunt, three or fewer chambers are involved. In patent ductus arteriosus, for example, only the chambers on the left side participate. In ventricular septal defect, three chambers are concerned, but the right atrium is not. In atrial septal defect the two atria and the right ventricle carry shunted blood, but the left ventricle does not enter into the process. In less common forms of intracardiac communication, such as an anomalous communication of the coronary artery with a cardiac chamber, or in ruptured aneurysm of an aortic sinus, only one or two chambers participate in the shunt, depending upon the chamber into which the abnormal communication occurs.

We have attempted to coin a descriptive name for the type of shunt found in this patient. The term "circular shunt" seems appropriate.

DR. SHONE: Dr. Lillehei, would you care to comment on the preoperative diagnostic



Fig. 6. *Left:* Interior of the pulmonary trunk and the unopened pulmonary valve viewed from above. The valve has a characteristic dome-shaped deformity, at the center of which is the stenotic opening. The picture is characteristic of the pulmonary valve in congenital pulmonary valvular stenosis. The pulmonary trunk is wide. *Right:* Right atrium and right ventricle. A widely patent foramen ovale is present. The valve of the foramen ovale is not visible. The tricuspid valve shows several abnormalities. These include an accessory opening (*arrow*) at the junction of the septal and posterior leaflets. There also is attachment of the septal leaflet (*S.*) to the ventricular septum below the annulus fibrosus, representing a mild degree of Ebstein's malformation. Vegetations of healed bacterial endocarditis are present on the contact aspect of the valve. The right atrium is moderately enlarged.



Fig. 5. *Upper:* Left ventricle and ascending aorta. At the junction of the membranous and muscular portions of the ventricular septum is a small ventricular septal defect (*point of arrow*). The wall of the left ventricle is hypertrophied. The cavity is moderately enlarged. There are vegetations upon the aortic valve cusps. *Lower:* Interior of the right ventricle. The probe lies in the ventricular septal defect, which lies above the papillary muscle of the conus (*P.C.*). Opposite the ventricular septal defect (*end of probe*) on the anterior wall of the right ventricle is a pale area which represents focal endocardial thickening. This change is considered to be due to the trauma of the shunt, which is assumed to have passed in a left-to-right direction through the ventricular septal defect. The right ventricular wall is moderately hypertrophied and is considerably less thick than the left.

it was considerably less thick than the left ventricular wall, being approximately from one half to one third its thickness. The right ventricular chamber was of normal size or possibly slightly larger than normal.

There were malformations in both valves related to the right ventricle. The pulmonary valve was the site of classic dome-shaped stenosis. The effective orifice at the apex of the dome was only 3 mm. wide (Fig. 6, *left*). The pulmonary trunk was enlarged, measuring about 3 cm. in diameter. The other valvular malformations involved the tricuspid valve (Fig. 6, *right*). The basal attachment of the septal leaflet was to the ventricular septum below the level of the annulus fibrosus. At the junction of the septal and posterior leaflets was a classic "double orifice" of the tricuspid valve. Fibrous vegetations of irregular nature were deposited along the contact surface of the leaflets. The right atrium was enlarged. The atrial septum showed a valve-competent patent foramen ovale with a potential opening of 3 cm. (Fig. 6, *right*). The vegetations on the tricuspid and aortic valves could be interpreted as representing healed bacterial endocarditis, although no history of this disease was given.

Tricuspid insufficiency is interpreted as having been present and to have resulted from two malformations: (1) the low attachment of the septal leaflet, representing a mild degree of the Ebstein malformation, and (2) the "double orifice."

From the anatomic observations of this heart, we can interpret the shunts this way: at the ventricular level a small ventricular septal defect would prevent free communication between the two chambers. In view of the greater thickness of the left ventricle, one would conclude that the shunt through the ventricular septal defect was in a left-to-right direction. Additional support for this interpretation is the jet lesion which was identified opposite the ventricular septal defect in the endocardium of the anterior wall of the right ventricle. The foregoing evidence favoring a left-to-right shunt through the ventricular septal defect appears to be sufficiently strong to be acceptable, even in the presence of the severe pulmonary stenosis.

coexistent ventricular septal defect, pulmonary valvular stenosis, congenital tricuspid insufficiency, and patent foramen ovale.

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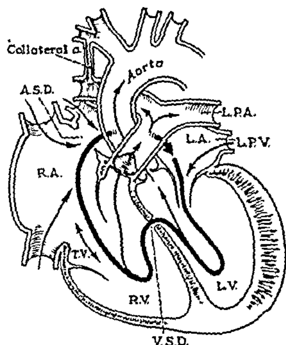


Fig. 7. Diagrammatic portrayal of the malformations in the case described and the assumed direction of the shunt. In essence, it is concluded that the shunt through the ventricular septal defect went in a left-to-right direction, and that, because of concomitant pulmonary stenosis and the tricuspid malformations, regurgitation occurred through the tricuspid valve. The right-to-left shunt (carrying fully oxygenated blood from the left ventricle) occurred at the level of the patent foramen ovale. From the left atrium the shunted blood then continued into the left ventricle and, beyond that, in the path already mentioned. The participation of each cardiac chamber in the shunt is an unusual phenomenon, and the type of shunt present here is named a "circular" shunt. *R.A.*: Right atrium. *A.S.D.*: Patent foramen ovale. *T.V.*: Tricuspid valve. *R.V.*: Right ventricle. *V.S.D.*: Ventricular septal defect. *L.V.*: Left ventricle. *L.A.*: Left atrium. *L.P.V.*: Left pulmonary veins. *L.P.A.*: Left pulmonary artery. *Collateral a.*: Collateral artery.

studies and on the type of operative procedure you would have elected in the light of the findings at necropsy.

DR. LILLEHEI: It is quite likely that catheterization of the left side of the heart with a left ventriculogram preoperatively would have clarified the diagnosis. It is for this reason that we have found studies of the left side of the heart to be particularly valuable. We recommend them in all patients with unusual congenital cardiac malformations when studies of the right side of the heart have left some doubt as to the precise anatomic diagnosis.[1-3]

In this patient, although a patent tricuspid valve and right ventricular cavity were present, the preoperative studies and the postmortem findings suggested that the characteristics of the circulation through the right side of the heart may have been similar in certain respects to those in tricuspid atresia. Although a palliative shunt of the subclavian-pulmonary artery type or Potts type has been recommended frequently for palliation in tricuspid atresia, it has become increasingly clear that routine use of a shunt in these patients may not be nearly so predictably helpful as it has proved to be in the tetralogy of Fallot. It even may be harmful. Patients with tricuspid atresia must have a shunt from right-to-left if they are to survive. Usually, this shunt occurs at the atrial level through a patent foramen ovale or atrial septal defect. Surgical creation of a left-to-right shunt of the Blalock or Potts types in these patients increases the pulmonary blood flow and increases the left atrial volume and pressure, which, in turn, may interfere with the right-to-left shunt. Since the beneficial effects of the surgically created left-to-right shunt depend entirely upon the continued presence of a right-to-left shunt, these patients actually may have the quantity of oxygen available to the body reduced rather than increased by the surgically created shunt.

In this particular patient, it seems likely that such a mechanism may have played a role in his poor response to the operation. In retrospect, it is obvious that it would have been better to perform a pulmonary valvotomy without any attempt at closing the ventricular septal defect at this stage.

For patients with tricuspid atresia of the usual type (with reduced pulmonary flow) the anastomosis of the superior vena cava to the right pulmonary artery[4] offers promise of better palliation by creating a direct increase in the flow of unoxygenated blood through the lungs. We believe, however, that a direct anastomosis of the main pulmonary artery to the right atrium with closure of the atrial septal defect[4] might accomplish this purpose even better. This procedure is under investigation.

Diagnosis: "Circular" shunt resulting from

tends below the dome of the diaphragm is a well-known sign of left ventricular enlargement (Fig. 3,*A*). In the left anterior oblique position (about 60 degrees) the enlarged left ventricle extends downward and posteriorly over the spine (Fig. 3,*B*). In the lateral view the left ventricle may project posteriorly to the barium-filled esophagus (Fig. 3,C). It should be emphasized that radiographic estimation of size is much more difficult and much less reliable for the left ventricle than for the right ventricle or left atrium. A normal-sized left ventricle may be displaced posteriorly by a large right ventricle, simulating left ventricular enlargement (Figs. 4-5).



Fig. 1. *A*, Marked displacement of esophagus to right on posteroanterior roentgenogram. *B*, Left atrial displacement not demonstrated on lateral film. *C*, Marked displacement of esophagus on the right anterior oblique view only.

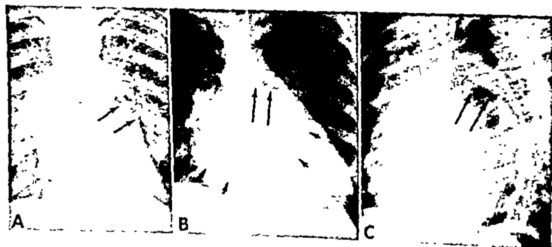


Fig 2. *A*, "Third bulge" due to distention of left atrial appendage. *B*, Double density (*short arrows*); note also the elevation of left main-stem bronchus (*long arrows*). *C*, Elevated left main-stem bronchus well demonstrated on left anterior oblique view.

The roentgenographic diagnosis of mitral and aortic valvular disease

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Radiographic techniques play an indispensable role in the diagnosis of cardiac valvular lesions. It is the purpose of this paper to summarize roentgenographic signs that are important in this diagnosis. Routine roentgenography and cardiac fluoroscopy give pertinent information, but often exact differentiation between stenotic and incompetent valvular lesions cannot be made by these means alone. The rapid advancement of cardiac surgery has called for the development of more specialized radiographic procedures which allow evaluation of valvular competence with a high degree of certainty.

Mitral heart disease

Mitral stenosis or insufficiency causes characteristic enlargement of cardiac chambers which can be demonstrated readily on routine heart films and by cardiac fluoroscopy. Both lesions result in left atrial and right ventricular enlargement. The size of the left atrium can be well assessed radiographically because of the close proximity of the left atrium to the esophagus. On the posteroanterior roentgenograms the barium-filled esophagus may deviate to the right or, rarely, to the left, or it may be undisplaced; consequently, the posterior displacement will be indicated more clearly either in the lateral or right anterior oblique views (Fig. 1). It is important that a complete series of heart films be obtained in deep inspiration, since enlargement of the left atrium may falsely be suggested in views obtained on expiration. Other signs of enlargement of the left atrium are those listed below:

1. A third bulge along the left heart contour which is due to distention of the left atrial appendage (Fig. 2,*A*): This finding in itself without other evidence of left atrial enlargement is not definitive since it may be observed on rare occasions in normal patients.

2. The increased angle of the tracheal bifurcation which is due to elevation of the left main-stem bronchus, which is best seen in the left anterior oblique view (Fig. 2, *B* and *C*): This sign is usually seen only if the left atrium is moderately or severely enlarged. Abnormal fullness below the left main-stem bronchus on the left anterior oblique view may be an early sign of left atrial enlargement.

3. The appearance on the posteroanterior roentgenogram of a double density, which is especially obvious if high-kilovoltage technique is used (Fig. 2,*B*).

Radiographically, the size of the right ventricle is more difficult to evaluate. The most important view is the lateral projection, which demonstrates an increased area of contact between the sternum and the right ventricle, together with elevation of the right ventricular outflow tract. For the differential diagnosis of mitral stenosis and insufficiency, evaluation of the size of the left ventricle is extremely important. On the posteroanterior roentgenogram a low, rounded apex which ex-

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reliable means of evaluating mitral competence. The catheter can be inserted into the left ventricle either in retrograde fashion through the aortic valve,[9] or through the atrial septum,[10] or in a direct percutaneous approach through the chest wall.[11] Transapical catheterization techniques are used only if the aortic valve cannot be passed in retrograde fashion. Retrograde aortic catheterization is the procedure of choice for the following reasons: (1) A catheter of adequate size can be placed in the left ventricle near the apex not in contact with the mitral valve. (2) The morbidity and mortality rate with transaortic catheterization is lower than with transapical catheterization. (3) The catheter is not passed through the valve to be examined as in the transatrial approach.

During left cardioangiography, contrast medium is injected into the left ventricle, and mitral incompetence is readily indicated by roentgenography or by cineradiography, appearing as opacification of the left atrium. At present, the degree of mitral regurgitation cannot be expressed in milliliters per minute, but it can be rated as Grade 1, 2, 3, or 4+ incompetence (Fig. 10). This semiquantitative estimation has proved to be pragmatically satisfactory since it provides a criterion for deciding whether closed-heart or open-heart surgery should be performed. In Grades 1+ and 2+ mitral incompetence the left ventricle is not significantly enlarged; posterior displacement of the left ventricle gives indirect evidence of enlargement of the right ventricle. The interventricular septum is seen on end on the lateral film studies because of rotation of the heart. The right coronary artery shows a sweeping course; it is usually large and projected anteriorly to the left anterior descending branch on the lateral film studies (Fig. 5). The distance between the sternum and the interventricular septum is increased, in keeping with enlargement of the right ventricle. In predominant mitral stenosis the angiographic studies are usually brilliant because of the decreased stroke volume of the left ventricle and consequent minimal dilution of contrast medium. In Grade 1 insufficiency, a minute regurgitating jet is well demonstrated, suggesting a small orifice with a minor element of incompetence (Fig. 11). In Grade 2+ mitral insufficiency the jet is larger and the opacification of the left atrium is more dense. Ballooning of a



Fig. 14. *A*, Rigid aortic valves with negative jet, suggesting acquired aortic valvular stenosis. *B*, Subvalvular ring. *C*, Supravalvular stenosis. Study performed by transthoracic catheterization. Note the huge coronary arteries characteristic of supravalvular stenosis.



Fig. 12. A, Aortic configuration with prominence of ascending aorta. B, Prominent ascending aorta well seen on left anterior oblique view (poststenotic segment). C, Increased pulsations of poststenotic segment are visualized on kymogram. Note also the aortic valvular calcifications (*circle*).

suggests predominant or pure mitral stenosis. The larger the cardiac silhouette and the larger the left atrium, the more likely the possibility of significant or even predominant mitral insufficiency. A giant left atrium is very commonly associated with massive mitral insufficiency, but there are also a few exceptions to this rule. If prominent Kerley lines are present at both lung bases, the predominant valvular component is very probably mitral stenosis. If no signs of aortic disease exist, left ventricular enlargement suggests mitral incompetence.

Angiographic procedures. The intravenous injection of contrast medium allows visualization of the right and left ventricles and comparison of their sizes. In mitral stenosis the right ventricle and pulmonary arteries are usually enlarged and the left ventricle is relatively small. The enlarged left atrium does not show significant change in size during ventricular systole and diastole. There is a hold up of contrast medium in the left atrium, with a delayed opacification of the left ventricle and the aorta. The only specific finding of mitral stenosis in forward angiography is "doming" of the stenotic mitral valve into the left ventricle[8] (Fig. 9). Mitral insufficiency, on the other hand, is characterized by enlargement of the right and left ventricles and usually by great enlargement of the left atrium, which may show considerable change in size during ventricular systole and diastole. "Doming" of the mitral valve is usually not observed. Since forward angiography does not allow exact differentiation between mitral insufficiency and mitral stenosis, its diagnostic usefulness is limited.

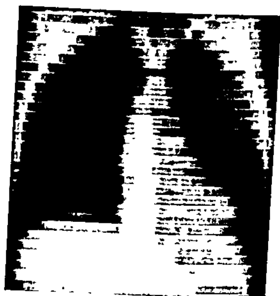


Fig. 13. Increased pulsations of descending aorta, suggesting aortic insufficiency. (In aortic stenosis, descending aorta shows normal pulsations.)

Left ventriculography is a much more

lent means of visualizing pulsations of the descending aorta which cannot be seen on fluoroscopy (Fig. 13).

Poststenotic dilatation of the ascending aorta is highly suggestive of valvular aortic stenosis, since this finding is almost invariably absent in supravalvular and subaortic stenosis. As in pulmonary stenosis, no definite correlation exists between the degree of poststenotic dilatation and the actual severity of aortic stenosis. Localization of the stenotic site and evaluation of the degree of stenosis are best accomplished by angiography and measurements of pressure. Retrograde catheterization of the left ventricle through the aortic valve is the preferred method, but successful passage of the catheter through the stenotic valve may not be feasible. In our experience, in 45 per cent of the patients with aortic stenosis the catheter could not be passed through the aortic valve into the left ventricle. This rather high incidence of failure probably occurred because the catheter was introduced exclusively through the femoral artery. Passage of the catheter from the right brachial artery or introduction percutaneously into the right subclavian artery[13] has a much higher incidence of success.

If the left ventricle cannot be entered in retrograde fashion, transseptal catheterization[10] may be performed, or a small Teflon catheter may be introduced by transapical left ventricular puncture.[11,14] The Teflon catheter can easily be manipulated into the aorta, and pullback pressures across the stenotic valve may be obtained. On some occasions the mitral valve may be assessed by the same technique. Left ventriculography is invariably performed in order to exclude the diagnostic possibilities of a significant subvalvular component of aortic stenosis and mitral incompetence. The subvalvular stenotic segment may be overlooked during surgical intervention in spite of digital exploration of the left ventricular outflow tract at the time of operation.

Radiographic signs of aortic stenosis on aortography usually include impaired motion of irregular and thickened, rigid valves with a negative jet during ventricular systole (Fig. 14). If the aortic valvular leaflets are fused and pliable, doming of the aortic valve may be seen during ventricular systole, particularly in cases of congenital aortic stenosis. No direct conclusion as to the severity of aortic stenosis and the appearance of the negative jet may be drawn. In patients with bicuspid aortic valves, all the angiographic and clinical findings of aortic stenosis may be present without a pressure gradient across the

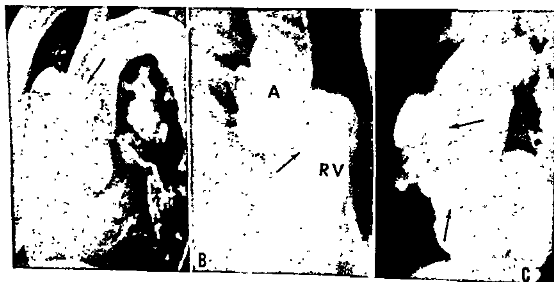


Fig. 16. Rare aortic "runoff" lesions best diagnosed by aortography. *A*, Coronary artery fistula to pulmonary artery. *B*, Ruptured sinus of Valsalva. Note the regurgitation of contrast medium from aorta (*A*) to right ventricle (*RV*). *C*, Aortic left ventricular tunnel, a rare form of aortic runoff.[11]



Fig. *15*. Aortogram showing 1+ aortic incompetence which was not suspected clinically (confirmed by operation)

fused stenotic mitral valve may cause a characteristic filling defect on the anteroposterior and lateral views[12] (Fig. 10,*A*). Since a similar deformity has also been observed in patients without mitral disease, and especially in the young age group, it is not considered to be an absolute sign of mitral stenosis.

In predominantly mitral insufficiency the enlarged, forcefully contracting left ventricle can be readily identified. There is dense, increasing opacification of the left atrium, which usually is markedly enlarged. In keeping with the hemodynamics of *mitral insufficiency and the* increased stroke volume of the left ventricle, considerable dilution of contrast medium occurs, and, consequently, the angiographic studies are less brilliant. In Grade 3 and 4+ mitral incompetence no regurgitating jet can be identified (Fig. 10,*B*).

After the left ventriculogram is taken, pressures are recorded across the aortic valve in order to exclude the diagnosis of aortic stenosis, and, invariably, aortography is performed in order to evaluate aortic valvular incompetence. This technique of left retrograde angiocardiography proved to be reliable in the evaluation of mitral competence in 600 patients examined at the University of Minnesota Hospitals. Excellent correlation was noted between the surgical and angiographic findings, except in 2 patients in whom a significant degree of mitral incompetence was found at surgery but was not demonstrated by left ventriculography. In spite of these two errors, which are not understood at this time, it is thought that a good left ventriculogram represents a most accurate technique in the evaluation of mitral incompetence.

Aortic valvular disease

Hemodynamically, aortic valvular disease is characterized by an increased load on the left ventricle. In the presence of pure aortic stenosis, which may be valvular, subvalvular, or supravalvular, the *hypertrophy of the left ventricle may* not be readily recognized on routine roentgenograms unless there is actual dilatation of the left ventricular chamber. As a matter of fact, severe aortic stenosis may be present, with a cardiac silhouette that appears to be essentially normal. In most cases, however, the well-known "aortic configuration" of the heart will suggest the correct diagnosis of aortic valvular disease. When valvular calcifications are absent, this defect cannot be definitively differentiated from arteriosclerotic or hypertensive heart disease on the appearance of the cardiac silhouette alone. Fluoroscopy and kymography allow differentiation between these lesions, and, in addition, differentiation between aortic stenosis and insufficiency with a high degree of accuracy. *Both types of aortic valvular* lesions show dilatation of the aorta. Aortic stenosis is characterized by specific dilatation of the ascending aorta (poststenotic), which shows increased pulsations on fluoroscopy and kymography (Fig. 12). Predominant aortic incompetence, on the other hand, manifests itself by mild uniform dilatation of the aortic arch and increased pulsations of the left ventricle and ascending and descending aorta. A kymogram is an excel-

Annotations

Cardiac malformation in Mongolism

When Down[1] distinguished Mongolism from other forms of severe mental retardation almost 100 years ago, he made no specific mention of heart malformation in the disorder. Since the end of the nineteenth century, publications on the topic have shown a variation in the proportion of Mongoloids affected by heart anomalies, the type of cardiac defect most commonly encountered, and the relationship of heart defect to early death. Most of these differences may be attributed singly or in combination to the small size of the sample, loading of the sample with hospital patients, autopsy data alone, or too few infant patients, and lack of uniformity in the criteria employed for clinical or pathologic diagnosis of the heart lesion. The majority of reports have been concerned with European populations, but Mongolism has also been found in African, Chinese, Indian, Indonesian, Jamaican, Japanese, Pakistani, and Thai individuals. Limited information suggests that heart malformation complicates the disorder in other races in much the same proportion as in the European.[2]

Two recent papers have approached the problem along rather different paths. One study[3] of 141 autopsies obtained over a span of 20 years in Mongoloids from one hospital for the mentally deficient, and from two obstetric and two pediatric hospitals in England, covered an age group from birth to 27 years. Fifty-nine per cent of the subjects were under the age of 12 months, and of the total number examined, 79 (56 per cent) were found to have congenital heart disease. The other,[4] a prospective study designed specifically to detect heart defect, assessed 174 Mongoloid infants and children, 71 per cent of whom were under the age of 12 months. They were seen as part of a counselling service over a recent 2-year period, and all received physical, chest x-ray, and ECG examination. The majority were studied by fluoroscopy with barium in the esophagus, and further study was requested in all cases. In the one third in whom permission was granted, cardiac catheterization was performed. Autopsy was obtained in 29 of 53 subjects who died during the study and follow-up period of 2 to 4½ years. Eventually, 70 (40 per cent) were found to have cardiac malformation. Both series satisfy requirements for relatively large numbers, with a majority of patients in the infant group. The chances are high that any large autopsy study of cases of Mongolism will show a bias toward subjects with associated severe malformation, and this point is emphasized by the fact that, in the Toronto group, congenital heart disease was found in 59 per cent of the 29 autopsies performed during the study. It seems probable that the examination of well Mongoloids who had no special reason to be hospitalized in the one series, and the inclusion of 60 malformed hearts from 90 autopsies of patients in children's hospitals in the other series make an important difference in the frequencies reported.

For years it has been known that septal defects, particularly defects of the atrioventricular canal, and ventricular septal defects were common in Mongolism. In the English autopsy group, defect of the atrioventricular canal, secundum atrial defect, and ventricular septal defect occurred in almost equal proportions, together constituting about 80 per cent of the 79 subjects with congenital heart disease. In the prospective study, defect of the atrioventricular canal and ventricular septal defect occurred in almost equal proportions, together constituting almost 70 per cent of the 70 patients with congenital heart disease. In the latter study, atrial defects of the secundum type were found only about one third as frequently as in the autopsy series. The explanation of this difference might appear to lie in the well-known difficulty of clinical diagnosis of secundum atrial defects in infancy. Despite the approach made in the Toronto study, it is conceivable that some examples went unrecognized, yet it is unlikely in the particular circumstances that the large difference could be explained fully on this basis. Whether varying interpretation of the presence of patency of the foramen ovale may have influenced the English figure is a pertinent question, particularly since the majority of cases of this defect were found at autopsy in infants. Other points of difference lie in the absence of isolated patent ductus arteriosus and aberrant right subclavian artery in the English series, whereas 10 and 7 per cent, respectively, of the total were accounted for by these malformations in the clinical study. It is easier to believe that these anomalies might have been either missed entirely in the case of the aortic arch branch or interpreted differently by pathologists in the case of the patent duct. Allowance for the more striking differences in the two groups would increase the over-all percentage with malformation to about 45 per cent in the clinical study and 65 per cent in the autopsy series.

A curious feature about the Mongoloid group is the uncommon occurrence of the classic forms of cyanotic heart malformation. Tetralogy of Fallot has been reported on fewer than twenty occasions,

aortic valve. The presence of a negative jet is, therefore, not necessarily evidence of hemodynamically significant aortic stenosis.

In our experience, aortography has proved to be the most reliable means of evaluating aortic incompetence. In this procedure, 30 to 45 ml. of contrast medium are injected through a large-bore catheter which is positioned a few centimeters above the aortic valve plane. Anteroposterior and lateral roentgenograms are made at five exposures per second, or cineradiographic studies are made. As in mitral incompetence the degree of insufficiency can be evaluated as ranging from 1 to 4+, although a gradation ranging from 1 to 8+ would be more accurate. We have noted excellent correlation between the surgical findings and the angiographic appearance of the regurgitating jet. In a large group of patients, aortic insufficiency was demonstrated by this technique and confirmed on surgical intervention, although the lesion was not suspected clinically (Fig. 15).

An important "fringe benefit" of aortography is visualization of the coronary arteries. The status of the coronary arterial system is important in any patient considered for surgical correction of his cardiac defect, and it is of special differential diagnostic interest in patients with aortic stenosis and clinical signs of angina.

Aortography is also invaluable in differentiating aortic insufficiency from other aortic "runoff lesions." As a matter of fact, some of these lesions can be satisfactorily diagnosed only by this procedure (Fig. 16).

Summary

The pertinent radiographic findings of mitral and aortic valvular disease were reviewed. The exact diagnosis cannot be made on heart films and cardiac fluoroscopy alone in a high percentage of the cases. Special techniques, such as aortography and left ventriculography, are very helpful and reliable in evaluating valvular competence.

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Regulation of blood pressure: A cybernetic mechanism residing in the kidney?

Recent evidence that two separate and opposing secretions from the pancreas serve to regulate blood sugar suggests that other important constants of the "milieu interieur" may be subject to a double control on the part of a single organ. The endocrine secretions of the kidney may well provide a second example, in this case as a regulating mechanism for control of the blood pressure.

There is ample evidence that under circumstances of reduced perfusion pressure the kidney secretes a pressor substance which serves to elevate systemic arterial pressure. Although the nature of the secretion has not been clearly identified, it would seem to be renin, which originates from the juxta-glomerular cells and, through direct and indirect mechanisms, releases a variety of less complex molecules, such as angiotensin and aldosterone, substances which serve to elevate the blood pressure. Studies of shock and of the response of blood pressure to nephrectomy or to renal vascular surgery leave little doubt that the kidney does secrete acutely and chronically a humoral pressor substance, although detection of it in the blood by our present methods is extremely difficult.

Evidence for a contrarily acting mechanism which originates in the kidney is also accumulating. The inhibiting effect of normal kidney tissue upon the development of renal "ischemic" hypertension is well recognized. Muirhead has located the cells which perform this function in the renal medulla, and he and Grollman have described an extract which, under special circumstances, has an antipressor effect. Milliez has recently isolated a substance from rabbit kidney medulla which has a prolonged antihypertensive action in the renal hypertensive rabbit. Furthermore, kidney transplants in man and animals rapidly normalize the blood pressure in cases of renal hypertension but do not produce hypotension. The kidney seems to stop releasing its antihypertensive secretion when the blood pressure reaches normal: Tobian has demonstrated in the rat that the depressor action of the normal kidney appears only when this organ is under increased perfusion pressure, whereas studies in our laboratory indicate that the depressor effect of kidney transplants, which is easy to demonstrate when the blood pressure is elevated by figure-of-eight ligation of the opposite kidney, does not lower the blood pressure of a normotensive animal.

These observations corroborate the intimate and reciprocal relationship between normal and "ischemic" kidneys which was described many years ago by Friedman and collaborators, further examined in the elegant experiments of Wilson and Byron on the "touched" and the "untouched" kidney, and recently extended by Gross, who has shown that the renin content of the contralateral kidney is reduced in the case of unilateral renal hypertension. This reciprocal relationship has been demonstrated in many other contexts since it was first described by Goldblatt in his classic experiments. A review of the literature and a presentation of some of the latest experiments in this field are referred to in a recent symposium, reprints of which are available on request to interested investigators.*

If indeed the kidney will some day prove to be the source of two oppositely acting secretions, both concerned with regulation of the blood pressure, of what importance would this conclusion be to the clinician and to the investigator? In the first place, such a finding would serve to reconcile the renal and

*Symposium on Experimental Renal Hypertension, University of Michigan Medical Bulletin 27:175, 1961. Reprints may be obtained by writing to Dr. Walter Freyburger, The Upjohn Company, Kalamazoo, Mich.

whereas transposition of the great vessels (with the exception of one study[4]) has been encountered only six times. Aortic coarctation, anomalies of the aortic valve, truncus arteriosus, mitral atresia, and pulmonary stenosis, although not unknown, are also rare.

Difficulties of clinical diagnosis in Mongoloids, since the great majority of those with cardiac malformations have septal defects, are naturally greatest during the neonatal period, a time when there is real advantage for prognosis in knowing with certainty whether serious heart malformation is present. At least in the Mongoloid subject the presence of a characteristic frontal plane *QRS* vector in the electrocardiogram will prove helpful in the recognition of a defect of the atrioventricular canal. In others of this age, caution should be exercised in *pronouncing subjects free of heart malformation.*[6] The suggestion that analysis of dermal configurations will show a low position of the palmar axial triradius in Mongoloids with heart defect would prove useful if confirmed.[4]

There appears to be a peak incidence of deaths from gross intestinal anomalies in the first month of life but, thereafter, heart disease is the prime factor which contributes to infant deaths in Mongoloid subjects. About two thirds of those who died in the first year of life in both studies mentioned had congenital heart disease. Similar conclusions were reached from a survey of 130 Mongoloids in Scotland.[7]

The discovery of trisomy 21 in the karyotype of Mongoloids[8] has led to a great surge of interest in genetic investigation of this disorder. In a majority of patients the condition appears to result from meiotic nondisjunction associated with late maternal age, and possible relationships between the trisomy and X-radiation,[9] hormone imbalance,[10] or infection[11] have been suggested recently. Heart defect has been both present and absent in proven cases of the regular type carrying 47 chromosomes. Mosaic forms 46/47 (so far none in association with heart defect)[12,13] and trisomy 21 with Klinefelter's syndrome *and congenital heart defect*[14] have already been reported. Variants due to translocation which involves chromosome 21 or 22 and one of those from group 13-15 or 21-22 have also been noted, the karyotype showing 46 chromosomes.[15] Some relatives of *Mongoloids* of this type have 45 chromosomes with the same fusion defect, and some of the families with repetition of Mongolism have been found to have this chromosome background. A proportion[16] but not all[17] of those with microsymptoms of Mongolism have this karyotype. Heart defect and normal hearts have been encountered in Mongoloids with the translocation anomaly. So far, it is not known whether there is greater frequency of cardiac malformation in any particular chromosomal type of Mongolism. Previous knowledge relating maternal age to the presence or absence of heart disease would suggest that no difference will be found.[4,18]

Autosomal trisomy has also been discovered in the chromosome groups 13-15[19,20] and 16-18.[21,22] These syndromes have several features which are parallel to those of Mongolism: mental retardation, an appearance which allows reasonably easy clinical recognition, a high incidence of heart defect (mainly ventricular septal defect), abnormal dermal patterns, and occurrence of mosaics and forms with extra sex chromosome.[23] Although trisomy is usually associated with widespread and serious bodily anomalies, it may occasionally produce less disturbance; the recent report of trisomy 19 with atrial septal defect in mother and child[24] is of great interest in this regard.

So far, the feverish activity in cytogenetics has not apparently allowed great pause to examine the question of interrelationships between heart malformation and trisomy, but this aspect must soon be considered in greater detail. It is to be hoped that such work may improve understanding not only of the mechanisms of production of heart defect in cases of Mongolism and other trisomic anomalies, but also give a glimpse of the origins of cardiac malformation in general.

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Corticosteroids in Stokes-Adams syndrome

The nature of the Stokes-Adams syndrome was first recognized in 1776,[1] and it was particularly well defined in 1927, when Parkinson[2] and his group classified these attacks in the following categories: (a) ventricular standstill; (b) ventricular tachycardia and ventricular standstill; (c) ventricular tachycardia or fibrillation, or both; and (d) extreme bradycardia due to heart block. Since that time, other cardiac conditions have also been recognized as capable of producing this syndrome, and DeBoer[3] has defined it as "every disturbance of the action of the heart that begins and ends abruptly and causes such interruption of the circulation that more or less complete cerebral ischemia results." Clinically, there may be all grades of disturbances of consciousness, from a mild lightheadedness or dizziness to complete unconsciousness with convulsions.

Ordinarily, the basic pathologic abnormality is arteriosclerosis with fibrosis which causes interference of A-V conduction or, in some instances, an irritable focus with the production of arrhythmias. As a result of the poor supply of blood, there may be ischemia or actual myocardial necrosis In other cases the defect may be due to a myocarditis of rheumatic or, very rarely, of diphtheritic etiology Interference with conduction and the production of arrhythmias may also result pharmacologically from the use of certain drugs, notably quinidine and digitalis.

Treatment of Stokes-Adams attacks has been attempted with many drugs, including epinephrine, ephedrine, isoproterenol, atropine, and molar sodium lactate. Quinidine and procaine amide have also been used, although in some instances they may actually precipitate episodes of ventricular tachycardia or fibrillation.[4] Recently, electrical pacemakers have also come into use.[5] The drug or procedure of choice is controversial. Robbin and associates,[6] and Schumacher and Schmock[7] believe that the drug to use is isoproterenol, but Zoll[8] and his group favor ephedrine or epinephrine for standstill or for a slow idioventricular rhythm.

At times none of these agents is effective. Recently, there have been several reports of the use of corticosteroids for the treatment of this syndrome. Prinzmetal and Kennamer[8] reported that, on two separate occasions, the use of ACTH terminated attacks of ventricular asystole and syncope in a patient who had a posterior myocardial infarction. Phelps and Lindsay[9] brought about abolition of complete A-V block through the use of cortisone intramuscularly in a patient who had anterior infarction. In another instance[10] a case of complete A-V block reverted to partial (3:1) A-V block, and, at the same time, episodes of syncope and convulsions due to ventricular tachycardia and standstill were abolished during the administration of oral cortisone. In this case there was reversion to complete A-V block, and death, when this medication was stopped. At autopsy there was fibrosis and calcification in the region of the A-V node and bundle of His, and there were also vascular scars which were thought to be due most probably to a previous rheumatic myocarditis.

The beneficial effect of the corticosteroids may be due to several possible mechanisms. There is good evidence that these agents have an anti-inflammatory effect. Massell[11, 12] and his group found that the corticosteroid-hormone treatment of 66 patients with rheumatic fever caused the prolonged P-R interval to revert to normal in 54 of them. There may also be a "biologic cooperation" between C-11-oxysteroids and the sympathetic nervous system, as postulated by Lown and co-workers,[13] who found a correlation between the urinary excretion of 17-ketosteroid and the A-V conduction time They studied a group of patients with Addison's disease and also another group with Cushing's syndrome, and found that those with Addison's disease tended to have long P-R intervals, and that, in some instances, there was first-degree A-V block, whereas many of those with Cushing's syndrome had definitely short P-R intervals. Gerisch and associates,[14] in a study of the effect of cortisone treatment in experimentally produced myocardial infarction in dogs, found that there was increased vascularity of the myocardium due to dilatation of the collateral arteries. The resulting areas of fibrosis in the infarction were smaller than those in the control animals. Also, no thromboses were seen in the smaller vessels of the treated animals, in contrast to the findings in the control animals. Gerisch and co-workers also treated a group of patients with myocardial infarction with cortisone and found that this group derived very definite benefit. Another factor which may be of importance in steroid treatment is the production of alkalosis. The presence of alkalosis has been postulated[15, 16] as the factor which makes possible the beneficial effect of molar sodium lactate. Houle[17] and his group found a diminished cardiac and pressor response to epinephrine in the presence of acidosis. Levels of serum potassium may also be important in relationship to the effect of the steroid hormones[18] However, administration of potassium has had a beneficial effect

renoprival explanations for the etiology of hypertension. In the second place, it might encourage investigators to look for the pathogenesis of essential hypertension in terms of a deficiency of the appropriate renal response to elevated blood pressure. In the third place, more widespread recognition of the antihypertensive role of the normal kidney should cause surgeons to hesitate to remove "ischemic" kidneys when revascularization is at all possible in the treatment of renal vascular hypertension. Finally, studies to isolate a hormone from the kidney which might regulate the blood pressure down to but not below the normal value would seem to offer more therapeutic advantages in the treatment of hypertension than the further development of nonspecific depressor substances. Discovery of such a substance in normal kidney tissue would introduce a new era in the treatment of hypertension comparable to that which followed the discovery of liver extract for the treatment of pernicious anemia. The significant investigations now proceeding in this direction deserve more attention than has so far been accorded to them in laboratories devoted to research in the problems of experimental and clinical hypertension.

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The use of steroids in pericarditis

Pericarditis tends to be a recurrent disease, whether due to viral or bacterial infections, surgical incision of the pericardium, trauma, actinomycosis, or after myocardial infarction.[1] Recurrences have been reported in as high as 63 per cent of the patients after mitral commissurotomy, but rates of 30 to 40 per cent have been more common.[2] Recurrences have been noted in 18 to 36 per cent of the patients after so-called idiopathic pericarditis.[3,4] In 100 patients who underwent open-heart operation for congenital defects, 30 per cent developed pericarditis after the operation.[5]

The predominant symptom is distressing pericardial pain, although pleuritis and pneumonitis may also occur. Rarely, the disability from recurrent symptoms has been so great that total pericardiectomy has been necessary for the patient to obtain relief.[4,7] Steroids have been of particular value in relieving pain. They may be effective at times when opiates are ineffective. Furthermore, they may lessen the dyspnea due to splinting of the chest, without the impairment of ventilation experienced with opiates. The antipyretic effect is beneficial but of secondary importance, except in the rare individual with high fever. In the critically ill child with acute rheumatic or other type of pericarditis, the response within 24 hours may be dramatic. The subsidence of tachypnea with slowing of the pulse rate, the disappearance of an anxious expression, improved appetite, and sense of well-being may be noteworthy.

The impression has been gained that the suppression of inflammation with lessened formation of pericardial fluid may decrease the likelihood of pericardial tamponade. Often the elevated venous pressure may decrease within several days. At the present time there are no data to indicate that the course of a given attack of pericarditis is shortened, and premature withdrawal of steroids often results in the "rebound phenomenon"[3] *with return of pain and fever.*

Steroids should be reserved for those who do not respond to salicylates, and those who are severely ill. They should not be used in those in whom tuberculous pericarditis is suspected. The fear that virus infection might be disseminated under steroid therapy has not been borne out.

Prednisone in doses of 40 to 60 mg. daily is usually effective and should be gradually reduced by trial and error over a period of 2 to 3 weeks. If symptoms return with decrease in dosage, the amount should again be increased. The administration of gradually increased doses of aspirin during the period of withdrawal may lessen the likelihood of rebound and shorten the course of therapy.

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Book reviews

HYPERTENSION. (A Mount Sinai Hospital Monograph). Edited by Milton Mendlowitz, M.D., New York, 1961, Grune & Stratton, Inc., 156 pages Price $6.50.

This little book is not, and is not intended to be, a complete treatise on all, or even the major, aspects of hypertension. It is a symposium on selected aspects of the subject by members of the staff of the Mount Sinai Hospital. It consists of 10 papers which vary in length from less than 4 to more than 30 pages, in annotation from 12 to 173 references, and, most importantly, in the level and depth of presentation. At one extreme are a short paper entitled "The Drug Treatment of Hypertension," which reports in a nonrigorous way on 167 patients, and the almost equally short and very general description of "Hypertension in Childhood," to which is appended one very interesting case report. At the other extreme are a paper on "The Diagnosis of Pheochromocytoma," which presents much hard to find detail with extremely complete documentation, and the final and longest paper entitled "Management of Hypertension in Pregnant Women," which reviews much data on the pathogenesis of this condition and cites alternative hypotheses without indicating preference.

A few comments are in order about individual chapters, particularly those likely to be used as a guide to therapy by physicians who do not specialize in hypertension. In the previously mentioned paper on drug therapy the authors present a useful clinical impression in regard to a heterogeneous group of patients treated for varying lengths of time. The opening paragraph makes the valid point that there are insufficient data to prove that currently available therapy will objectively benefit any except those with accelerated hypertension. Although the authors make a plea for the accumulation of data on large groups of patients with less severe hypertension, their failure to define rigorous criteria, particularly in categorizing the severity of the pretreatment hypertension or the degree of control during therapy, limits the usefulness of their observations in this regard The criterion used by the authors for a good therapeutic result was not control of blood pressure alone, but rather asymptomatic control of blood pressure. This highly desirable criterion is rarely fulfilled during the demonstrably effective treatment of accelerated hypertension. Finally, although the authors conclude with the optimistic note that the addition of guanethidine, bretylium, and the benzothiadiazines has produced "definite" improvement in the treatment of nonaccelerated primary hypertension, their "good results" only increased from 42 to 45 per cent.

The paper on "The Clinical Evaluation and Management of the Hypertensive Patient" does little to clarify a complicated and confused subject. For instance, the paragraphs at the bottom of pages 34 and 35 contradict each other, the first saying "These simple clinical procedures usually . . . differentiate . . primary . . . from secondary hypertension," and the second saying "The most difficult . . . problem . . . is . . . differentiation of chronic renal disease from essential hypertension." There are other small points which can be questioned, such as whether it is indeed possible to obtain a meaningful *Regitine test* when a patient's diastolic pressure is just over 90 mm. Hg.

The papers on "Hypertension in Childhood" and on "Surgical Considerations in the Treatment of Hypertension" consist largely of case reports. In the first paper, the first report is fascinating and the excellence of the result in a very grave situation is thoroughly worth emphasizing. The other three reports, particularly the last two, are of less interest and are less well documented In the second paper, it is surprising to find the first case designated "essential hypertension"; this patient had been hospitalized four times with glomerulonephritis, the last time being only 1½ years before hypertension was discovered.

This book will be of limited value to the physician who is seeking guidance in treating the usual hypertensive patient It will be useful, however, to one who wishes to delve a little deeper into the current thinking on specific problems in the field of hypertension.

LIVE HIGH ON LOW FAT By Sylvia Rosenthal, with a foreword by Jeremiah Stamler, M.D., Philadelphia and New York, 1962, J. B. Lippincott Company, 328 pages Price $6.75.

Live High on Low Fat is the latest of a series of medically oriented cookbooks concerned with the dietary theory of the pathogenesis of coronary heart disease. As such, and because of its title, the reception by medical people may be mixed, skeptical, and curious However, this book bears a mark of approval from the distinguished scientist who wrote the foreword. In addition, the obvious sincerity, informed opinion, and culinary know-how of the authoress, a physician's wife, is quickly reassuring.

Dr. Stamler has a great knack of summing up. In three pages he digests the problem of the American coronary epidemic and elaborates the personal characteristics of men for which there is evidence of a real relation to coronary risk—elevated level of serum cholesterol and blood pressure, obesity, excessive cigarette smoking, physical indolence, and clinical diabetes mellitus. He adopts the pragmatic concept that all of these related factors can be controlled or modified, and that modern nutritional science should provide an important part of an [illegible] able approach to the prevention [illegible] disease. He derives an informed [illegible] the coronary [illegible]

in abolishing A-V block in some patients although increasing the degree of block in others.

In summary, although the rationale for the use of corticosteroid hormones in selected cases of Stokes-Adams attacks is as yet unclear, there are several different possible beneficial mechanisms; these include: (a) the improvement of collateral circulation, (b) a specific antiinflammatory effect, (c) the production of alkalosis, and (d) the "specific cooperative effect" in conjunction with the sympathetic nervous system. The relationship and relative importance of these various factors is not yet well defined, and others may be still unrecognized. However, in selected cases of heart block and Stokes-Adams attacks, when conventional treatment methods have been ineffective, the use of corticosteroids seems to be indicated and may be beneficial.

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which is probably a reflection of a lack of knowledge and data. Most of the presentations seem to accept the idea that anatomic changes with age is consonant with the aging process. This may be true to some extent, but surely is not entirely true nor always possible to know when it is or is not true. For example, the chapter on aging changes in blood vessels is particularly representative of this failure. Section F on page 55 on the vasa vasorum states: "As part of the aging changes, vasa vasorum grow into the media of the aorta from the adventitia. These capillaries are found mostly in the outer third of the muscular layer, although they may extend to the middle third."

That is the entire presentation of a subject that has aroused the interest of many investigators concerned with the development of arteriosclerosis. Furthermore, no references are given to document the paragraph nor are quantitative data given. As written, the concepts are presented to suggest that the vasa vasorum are capillaries only. Such a paragraph is useless to the reader and would have been better if it had not been written. If the reader is interested in anatomic changes in man associated with chronologic age, this book can serve as a beginning of his review of the subject. Some chapters are better than others, however.

Unfortunately, this book contains many such loose statements which have been made by some authors who are not experts in the field. Because of a lack of a good source of collected data on the anatomic and pathologic changes associated with the aging process, one may wish to use this book for information on the aging process, but he is warned to do so cautiously and to know more about the source of the data and the qualifications of the author. The chapters vary in quality and value to a reader. Maybe in the next edition the Editor will have scholars and students of the aging process to write all chapters. Such a book is needed, but it must be of high quality.

Survey Report of the Cerebral Vascular Study Group, Institute of Neurological Diseases and Blindness, National Institutes of Health. St. Louis, 1961, Bargett Printing and Publishing Company, 139 pages.

This report was prepared by a committee of seven members, with Dr. James L. O'Leary as Chairman, 13 consultants, and 4 representatives of the National Institutes of Health, a group eminently qualified to do this work. Its purpose is to advise and aid the Institute of Neurological Diseases and Blindness in planning a continuing program in the cerebral vascular field.

The report is assembled in three sections: I. Introductory Statement for the Lay Reader. II. Present Knowledge of Cerebral Vascular Disease III. Desiderata and Recommendations.

The main body of the survey is found in Section II, which begins with a brief statement concerning the general problems in research and training and is followed by a dozen subdivisions, each concisely stating the contributions, recent advances, and current problems in the various areas of both basic and clinical fields of study. Not only are these excellent summarizations, but each is documented with an extensive bibliography which furnishes especially citations of recent publications.

Among the specific recommendations made are: the setting up of a permanent committee to program and implement a continuing research effort in the cerebral vascular area; provisions for up-to-date source books on current literature; cerebral vascular conferences—workshops to provide for exchange of information; training programs for specialized scientific personnel; expansion of research in areas of basic science as well as in all clinical phases, and an integrated basic and clinical endeavor.

This is a very instructive concise survey.

Drugs Affecting Lipid Metabolism. Edited by S. Garattini and R. Paoletti. Proceedings of the Symposium on Drugs Affecting Lipid Metabolism, Milan, Italy, 1960. Amsterdam, 1961, Elsevier Publishing Company, 604 pages. U. S. distributor, D Van Nostrand Company, Inc, Princeton, N. J. Price $19.50.

The talks given at the Lipid Congress in 1960, at Milan, Italy, are published in this book and are very informative. A wide range of material is presented, from the basic synthesis and metabolism of fatty acids to drugs that affect serum lipids both in animals and human beings. Therefore, this book could be profitably studied by basic science workers as well as physicians treating patients This is one of the few books that contain information about results with the many hypolipemic agents now available, such as the hormones and their analogues, heparin and heparin-like substances, unsaturated fatty acids, special phospholipids, psychotropic drugs, nicotinic acid and its derivatives, and several agents that may be new to the reader. The information is complex because of the many different animals used, the wide variety of methods used to measure the lipids, the complex designs, and the variety of problems that were investigated.

One is left with a large number of isolated facts about lipids and the awareness of the great potential of synthesizing them into concepts that will explain problems in both health and disease of human beings and animals.

Smoking and Health (Summary and Report of the Royal College of Physicians of London on Smoking in Relation to Cancer of the Lung and Other Diseases). New York, 1962, Pitman Publishing Corporation, 70 pages Price $1.

In 1959, the Royal College of Physicians set up a committee to report on the question of smoking in relation to carcinoma and other diseases.

to 50 per cent by the very feasible alteration of a single variable, an average reduction of 15 to 20 per cent in serum cholesterol of the adult American male.

The nutritional philosophy of the book is condensed by Dr. Stamler to the following tenets:

"Emphasizing the low-fat dairy products (skim milk, buttermilk, cottage cheese), and de-emphasizing the high-fat (sweet cream, sour cream, ice cream, whipped cream, cheeses, butter).

"Emphasizing the lean cuts of meat and poultry, and de-emphasizing the fat cuts, with trimming off fat before cooking, cooking so as to get rid of fat (broiling, rotisserizing, roasting with discarding of drippings, letting stews and soups stand in the refrigerator overnight with skimming off congealed fat), use of vegetable oils in braising meats etc., moderation of meat portion size (four to six ounces, not twelve to sixteen').

"Emphasizing fish and sea food, de-emphasizing eggs.

"Emphasizing vegetable oils, and de-emphasizing solid table spreads (butter, margarines) and solid shortenings (lard, suet, hydrogenated vegetable fats).

"Emphasizing fruit desserts (citrus and noncitrus), and de-emphasizing commercial cakes, pastries, shortcakes, cookies, and pies.

"Emphasizing green and yellow vegetables and legumes (peas, beans).

"Emphasizing moderation in use of starches (potatoes, rice, spaghetti, breads, cereals), carbohydrate-rich spreads (jellies, jams, honey, marmalade), alcoholic beverages."

Mrs. Rosenthal presents a very brief text on the diet objectives of the book in sections on "Cholesterol," "The Prudent Diet," and "The Battle of the Bulge." A good deal of opinion is expressed here, but it is largely well founded and does not smack of faddism or rash medical counselling.

Of the approximately 300 pages, 250 are devoted to her specialty of recipes. A well-known dietician who is involved in the field of coronary epidemiology, as well as my wife, helped evaluate the culinary soundness of Mrs. Rosenthal's volume, and the consensus was that many of the recipes were most promising, and that all were worth trying.

Each major food category is well treated. Sources of supply are given for items not universally available. Preparation of easily preservable mixes is outlined. One of the problems in converting from stiff fats to liquid oils in baking and food preparation is lessened by a helpful table of equivalent portions.

Starting with soup, that gourmet delight Vichyssoise is produced in fascimile with a cream of potatoes, skim milk and flour, and total absense of heavy cream.

The meat section provides enticing fare but completely ignores lean pork products, which, in fat composition, are not significantly different from, nor inherently "worse" than, beef, and which are consumed in almost equal amounts by the U.S. public. There is a host of excellent recipes involving veal, but I am informed that there are large areas out of urban centers where tastes are not educated and butchers do not even supply it. Pre-preparation of meat dishes allows easy separation of congealed fats, but my consultants resisted the idea, without performing the experiment, that pot roast would turn out as tasty if cooked the day before.

The balance struck in the book is reasonable and intelligent, but nowhere evinces the austerity of real low-fat cookery, although it is low in saturated fat. There are even instructions for making "cream" and "whole milk" with oil and butter flavoring, if you like.

At the conclusion are useful sections on spices, lists of "do's and don'ts," food composition and calorie tables, a cooking glossary, and a bibliography.

In general, the volume provides more recipes and less medical education than its outstanding predecessor *Eat Well and Stay Well* by Ancel and Margaret Keys (Doubleday), but both make sound recommendations to patients, precoronary as well as postcoronary.

In a recent talk to an industry group, I was a bit taken aback by the comment of an executive: "You docs are always taking things away from us, always saying 'don't' instead of 'do.' In my business if we discover we have a bad idea or poor product we darn quick come up with better ones." And that is really the purpose of this book, to provide as many "do's" as "don'ts," in an attempt to replace our immature luxus U. S. eating habits with more physiologic ideas in the form of more delightful dishes.

The price tag, I fear, is typical of our times, at $6.75.

STRUCTURAL ASPECTS OF AGING. Edited by Geoffrey H. Bourne, M.D., F.R.C.P., Department of Anatomy, Emory University Medical School, Atlanta, Ga.; Assistant Editor, Eileen M. H. Wilson. London, 1961, Pitman Medical Publishing Company, Ltd. 419 pages. U. S. distributor, Hafner Publishing Company, New York. Price $20.

Of the many contributors to this monograph, most are pathologists and anatomists from the United States, some are from England, and one is from Germany. The subjects include aging changes in the lymphoid and myeloid tissues, skeletal muscles, joints, smooth muscles, blood vessels, alimentary tract, salivary glands and pancreas, cartilage and bone, ovary, connective tissue, nerve cells, liver, blood cells, skin and related structures, thyroid and pituitary glands, eye, cell, adrenal gland, heart, teeth and sex glands.

This is not a very good monograph. The presentations are almost entirely descriptive and contain little discussion of the mechanisms of aging. Furthermore, the discussions are very brief at times (e.g., aging of lymphatic tissue),

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Editorial

Rheumatic fever and rheumatic heart disease as seen in the tropics

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The role of geography and climate upon the incidence, pathogenesis, clinical picture, and morbidity of rheumatic fever and rheumatic heart disease continues to be a controversial subject of great interest. Some authors have adduced evidence which points to significant differences in the illness related to geographical, climatological, and seasonal variations.[1,2] Others have felt so strongly about this matter that patients from temperate zones have been transferred to tropical areas in an attempt to improve or alter the progress of rheumatic fever or its complications.[3] Observers of the disease who reside in tropical countries have questioned the presence of fundamental differences.[4-8] Reliable comparative studies which present the relative incidence and the prevalence of the disease in different tropical and temperate areas of the world are few since, unfortunately, rheumatic fever and rheumatic heart disease are not reportable diseases in most countries of the world

Most of the studies on the rheumatic state refer to the prevalence of this disease in selected groups of the population. The proportion of people reported to be suffering from the disease in different populations has been variable, but the evidence available in autopsy studies and well-documented clinical observations reveal that there is a significant prevalence of this disease in different tropical communities of the world. The evaluation of the possible influences of geography and climate upon the disease is made more difficult because the data presented from different areas of the world lack uniformity in the selection of the clinical material. The incidence has been expressed in different forms, including clinical cases encountered per total hospital admissions, per total hospital nonsurgical admissions, per total rural and or urban population, and on the basis of a physician's personal private practice. A representative example of the clinical data presented in various areas of the world is shown in Table I. In these representative series, differences in the selection of clinical material and in the size of the sample can be noted. The various percentages of rheumatic heart disease encountered in areas with different climatological conditions are included. Observations made in New England by the same examiner during 1925 and 1950 show an apparent decrease in the relative importance of rheumatism as a cause of heart disease.

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This book written for doctors and laymen is the subject of that report. In it are recounted the history of tobacco smoking in Britain from the time of its introduction in 1590, a review of present smoking trends, a discussion of the evidence for and against the hypothesis that smoking is the cause of various diseases, and recommendations for preventive measures in the light of present evidence.

Several facts of interest are brought out in this report. There has been an increase in the number of people smoking in recent years so that now three quarters of the men and half of the women in Britain smoke. Also, more school children smoke than ever before. Along with this has been a steep increase in the expenditures on advertisement of tobacco. In reaching their conclusion that cigarette smoking is an important cause of lung cancer the authors site evidence from several statistical reports, both retrospective and prospective, as well as experimental studies on the carcinogenic substances found in tobacco.

Evidently, chronic bronchitis is a more serious and prevalent disease in Britain than in the United States, and the authors regard smoking as a conditioning factor in its production. Smoking is discussed with relation to diseases of the heart and blood vessels, gastrointestinal diseases, carcinoma of the bladder, cirrhosis, diseases of the central nervous system, and industrial accidents. In all of these there is some evidence of an association with smoking, but no direct causal relation could be established as the authors believe has been done with cancer of the lung.

The authors conclude that there is no evidence that smoking promotes physical health, its psychological and social benefits are hard to define, and, because of its proven harmful effects, they propose certain preventive measures. These include regulation of filters, modification of the tobacco itself, and, most important, an educational campaign to discourage smoking. They call upon the government for public education to draw attention to the hazards and to increase the tax on tobacco. A special plea is made to the doctors to urge their patients to stop smoking.

One can hardly read this report without becoming convinced of the causal relationship between smoking and cancer of the lung.

Announcement

The University of Texas Postgraduate School of Medicine is pleased to announce a course in DEDUCTIVE ELECTROCARDIOGRAPHY, to be conducted by the celebrated electrocardiologist, Dr. Demetrio Sodi-Pallares, of the National Institute of Cardiology, Mexico City. The course will be held on the evenings of Monday through Friday, Dec. 3-7, 1962, in the auditorium of The University of Texas M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, Tex.

This course will be profitable to both elementary and advanced students.

For further information write: Office of the Dean, The University of Texas Postgraduate School of Medicine, 102 Jesse Jones Library Bldg., Texas Medical Center, Houston 25, Tex.

Erratum

In the article "The Electrocardiographic Recognition of Left Ventricular Hypertrophy," by I. Rosenfeld, M.D., C. Goodrich, M.D., G. Kassebaum, Ph.D., A. L. Winston, M.D., and George Reader, M.D., which appeared in the June, 1962, issue of the Journal, mention was omitted of the "original electrocardiographic criteria for the recognition of left ventricular hypertrophy in the standard leads proposed by Gubner and Ungerleider in 1943."

in native-born indigent Puerto Ricans it was found that 871 persons died primarily of heart disease. Seventy-three of these deaths (8.4 per cent) were due to rheumatic heart disease. In this study, rheumatic heart disease still constitutes the most common cause of cardiac death in the age groups of 11 to 30 years.

According to the experience of most investigators in tropical zones, the clinical picture of the acute rheumatic state is similar to that reported in temperate countries.[6,7,31] No significant difference has been claimed by observers of the disease in the tropical or subtropical zones of Puerto Rico,[6] Jamaica,[7] Costa Rica,[8] and East Pakistan.[32] A few investigators living in the tropics have remarked that rheumatic heart disease is common in their countries but that acute rheumatic fever is rarely seen.[10,33] An adequate explanation for this phenomenon has not been presented. In countries like Mexico which have both temperate and tropical zones a difference in the relative prevalence of this illness in areas with different climates has been recorded, but no striking difference in the clinical manifestations of acute rheumatic fever in these areas has been mentioned.[12]

In Puerto Rico,[6] Jamaica,[7] and East Pakistan[32] the onset of the first episode of arthritis has been most frequent in the earlier decades of life. Manifestations in the joints have started in the weight-bearing joints of the lower extremities. The involvement of the joints has been polyarticular and of the migratory type. In our series of 101 native-born adult patients in Puerto Rico with acute rheumatic fever, all had had articular involvement, whereas out of 199 adults with rheumatic heart disease, 134 had had symptomatology which pertained to the joints. Manifestations in the skin and rheumatic nodules occurred in a low percentage of the patients. About 8 per cent of the patients had chorea. The severity of the symptoms pointing to cardiac involvement in the acute rheumatic state has been similar to that reported in some temperate zones.

The disease is described more frequently in females, although in studies from tropical East Pakistan[32] it has predominated in males. There is a predilection for involvement of the mitral valve, either alone or in association with the aortic valve. In Singapore[18] a relative higher incidence of aortic stenosis was observed. In Ceylon,[27] aortic insufficiency predominates over aortic stenosis. Complications of rheumatic heart disease have included congestive heart failure, atrial fibrillation, subacute bacterial endocarditis, and pulmonary or peripheral emboli. The most common cause of death has been congestive heart failure. In all instances, rheumatic heart

Table II. Autopsy data

Place	Year	Author	Total autopsies	Cardiac deaths: Total number	Cardiac deaths: Percentage rheumatic
Minnesota	1941	Clawson[22]	30,265	4,678	18.6
Ohio	1941	Scott and Garvin[23]	6,548	720	15.1
Ohio	1948	Wartman and Hellerstein[24]	2,000	984	13.0
Spain	1950	Ortiz-Vázquez[8]	3,000	—	34.5
South Africa	1946	Becker[24,25]	1,000	1,385	7.7
New Orleans	1945	Holoubek[26]	8,313	1,045	11.1
Uganda	1954	Williams, et al.[14]	1,773	231	8.7
Ceylon	1939	Fernando[27]	1,300	178	3.6
Costa Rica	1949	García-Carrillo[8]	8,000	768	18.0
Singapore	1957	Muir[18]	12,406	1,894	8.3
Jamaica	1958	Tulloch[11]	1,258	195	13.3
Puerto Rico	1944	Koppisch[6]			20.0
Puerto Rico	1961	Galindo[28]			8.4

Table I. Clinical rheumatic cardiovascular disease

Place	Year	Author	Total cardiacs	Percentage rheumatic	Source of patients		
					Hospital		Private
					Inpatients	Ambulatory	
New England	1925	White[9]	3,000	39 5	X	X	X
	1950	White[9]	3,000	23 5	X	X	X
North China	1957	Wan, et al.[10]	1,415	33 7		X	
Buenos Aires	1943	Cossio[11]	10,000	18 1	X	X	X
Mexico	1942	Chávez[5]	2,400	41 0	X		X
Mexico	1955	Salazar-Mallén[12]	26,091	33.4	X		
Tennessee	1933	Laws[13]	645	10 5	X	X	
Turkey	1959	Vural[14]	3,245	27 3	X		X
Texas	1953	Hutcheson, et al.[15]	1,000	6 5	X	X	
Uganda	1954	Williams, et al.[16]	167	9 0	X		
Northern Nigeria	1956	Beet[17]	358	23 0	X		
Singapore	1950	Monteiro[18]	208	14 1	X		
Jamaica	1958	Tulloch[19]	254	15 4	X		
Puerto Rico	1945	Suárez[4]	1,081	17 4	X		X
Puerto Rico*	1959	Ramírez[20]	722	12 2	X		

*Male veterans only.

The comparison of the data from different national sources becomes more complicated because some reports present cases of acute rheumatic fever exclusively, others present cases of rheumatic heart disease, and in certain instances both are presented together. The criteria used for diagnosing acute rheumatic fever have not been clearly stated in some of the studies. In other reports it appears that the diagnosis has been inaccurate if, to corroborate it, we apply the modified Jones' criteria recommended by the American Heart Association. The lack of a specific laboratory test for the recognition of acute rheumatic fever has handicapped the establishment of a definite diagnostic criterion with world-wide uniformity.

The postmortem anatomic diagnosis of rheumatic heart disease is more reliable. Table II illustrates a selected representative series of autopsy reports from different geographical areas. Although in some countries the mortality figures have not bee[illegible] impressive,[27] the problem is by n[illegible] important if we [illegible]sider the [illegible]e illness. [illegible] autopsy dat[illegible] cardiac d[illegible]

to rheumatic heart disease in the tropical areas of Puerto Rico,[4,28] Jamaica,[19] Costa Rica,[8] and Singapore,[18] reveals a significant contribution of this illness to the total mortality from cardiac ailments. As in temperate zones, rheumatic heart disease has occurred most frequently in the younger age group. In a large number of countries with different geographical and climatological conditions, such as the United States, England, North China,[10] Jamaica,[19] Cuba,[29] Puerto Rico,[4,28] Mexico,[5,12] Algeria,[30] Turkey,[14] Costa Rica,[8,31] and Africa,[24,25] rheumatic heart disease constitutes the most common cause of acquired cardiovascular disease in the younger age groups. Reports from Algeria[30] and Turkey[14] present rheumatism as the most common cause of cardiovascular disease.

In Puerto Rico, Koppisch, in 1944, reported that, in a series of 1,259 consecutive autopsies, death in 128 cases was found to be due primarily to cardiovascular causes. Twenty per cent of these deaths were caused by rheumatic heart disease. Clinical studies by Suarez revealed a similar incidence.[4] In a recent series of 3,600 consecutive autopsies from 1958 to 1961,

The presence of untoward external environmental conditions, such as overcrowding, inadequate clothing, poorly heated and ventilated dwellings, inadequate income and diet, upon susceptible individuals who have lowered body defenses apparently is an important contributing factor in the development of the disease anywhere in the world. The highest incidence of the illness is in poverty-stricken areas, regardless of geography and climate.

The impression of most authors who reside in the areas of Puerto Rico, Jamaica, Costa Rica, and East Pakistan has been that there are no striking differences in this disease as compared with its occurrence in temperate zones. A review of the available data indicates a possible inequality in the distribution of rheumatic fever and rheumatic heart disease in some tropical zones as compared to temperate regions. In view of insufficient controlled studies it cannot be stated definitely that these differences in distribution are brought about by conditions of climate and geography alone.

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disease constituted the most common cause of heart disease during pregnancy. No significant racial predisposition was encountered in Puerto Rico,[6] South Africa,[24] China,[10] and Jamaica.[7] These studies included patients who were of African, Caucasian, East Indian, Chinese, and mixed races.

In Puerto Rico[6] and Jamaica[7] a higher incidence of arthritis in the spring and winter, with a decrease in the autumn, has been encountered. This coincides with the variations usually reported in temperate climates. The explanation for this seasonal variation in tropical areas is difficult since, in a large number of these communities, only minor seasonal alterations in climate occur. In Jamaica and Puerto Rico, which are at about the same latitude, the difference between the average temperatures of the coolest and warmest months is about 6°F. In India no significant seasonal variations in the occurrence of rheumatic fever has been encountered.[35] In subtropical Mexico the majority of initial attacks occur during late spring and summer, and the lowest during winter.[12] Studies which present seasonal incidence or variations of Group A beta hemolytic streptococcal infections in the general population are not available in most of these areas. That seasonal variations are probably not related to cold and dampness was shown during World War I, when rheumatic fever occurred less commonly in troops in cold, damp trenches than among those stationed in warmer and drier but overcrowded areas. The outbreaks reported among healthy military recruits after epidemics of streptococcal sore throats and scarlet fever certainly tend to shift the importance to the common denominator of the presence of streptococcal infection apparently favored by certain external and internal conditions.

Early studies on the adult population in Puerto Rico revealed a low incidence of Group A beta hemolytic streptococcal infections, but recent studies by the same investigator, which included asymptomatic school children, have revealed that Group A hemolytic streptococci are commonly encountered in Puerto Rico.[36] The results of Dick testing in Puerto Rico in 1936 and 1959 were comparable to those reported in temperate zones. Median antistreptolysin titers of serums from a representative group of native-born Puerto Rican soldiers and those from North American troops from a temperate zone who were stationed in Puerto Rico did not show a significant difference.[37] Results of gel-diffusion studies on the antibody content of sera from Puerto Ricans, against components and metabolic products of Group A streptococci, have been comparable to those of similar studies carried out in the northern United States.[38] In Mexico, throat cultures were performed in two groups of students. One group came from a tropical and rainy area, and the other from Mexico City, which has a temperate climate. No significant difference in the incidences of Group A beta hemolytic streptococcal infection was found in these two groups.[35]

To evaluate the influence of climatological and geographical conditions upon rheumatic fever and rheumatic heart disease has become a somewhat more elusive matter in recent years. In countries with better social and economic conditions, where good preventive and educational measures and early treatment of streptococcal infections has been present, there has been an apparent decrease in the incidence, severity, and mortality of the disease.[39-44] The same observation has been made in the subtropical area of Mexico.[12] In certain areas of the world the incidence and death rate of the disease had decreased before the advent of the antibiotics, which suggest that, although important, this was not the only governing factor. Accumulated evidence has shown that adequate and early treatment of initial streptococcal infection decreases the frequency of acute rheumatic fever and that chemoprophylaxis reduces the incidence of rheumatic recurrences. It is interesting to note that in Denmark, although the incidence of streptococcal infection has increased, rheumatic fever has become less frequent.[44]

In spite of the apparent favorable changes in the illness in recent years, the available data certainly suggest that rheumatic fever and rheumatic heart disease are still an important health problem in tropical areas as in the temperate zones.

Clinical communications

Acute bacterial endocarditis at the University of Minnesota Hospitals, 1939-1959

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The authors of recent reviews of bacterial endocarditis report mortality rates of less than 60 per cent in acute bacterial endocarditis,[1,2] and less than 30 per cent in the subacute form.[3,4] These results appeared to be at variance with the experience of some members of the staff of the Department of Internal Medicine at the University of Minnesota Hospitals. They suspected that higher mortality rates had been encountered, especially in their patients with acute bacterial endocarditis. It is recognized that clinical impressions can be misleading. The most severely ill and unusual patients are remembered and the others sometimes forgotten. In order to obtain more information, a review of patients who had bacterial endocarditis at the University of Minnesota Hospitals during a 21-year period was undertaken.

Method

The University of Minnesota Hospitals record of each patient who was said to have bacterial endocarditis in the 21-year period between Jan. 1, 1939, and Dec. 31, 1959, was reviewed. There were 238 patients with this diagnosis. In 17 instances the evidence was inadequate to support a diagnosis of bacterial endocarditis; these patients were excluded from the present study.

There were 167 patients with subacute bacterial endocarditis. Subacute bacterial endocarditis is defined as a bacterial infection of the endocardium (valvular and or mural) which gives rise to symptoms which last 50 or more days, associated for the most part with a microorganism of low virulence, and having a chronic clinical course. This series of patients has been analyzed in detail.[5]

The present paper is concerned with an evaluation of acute bacterial endocarditis in the other 54 patients. Acute bacterial endocarditis is defined as a bacterial infection of the endocardium (valvular and/or mural) which gives rise to symptoms which last less than 50 days, associated for the most part with an invasive microorganism, and having a fulminant clinical course.

The analysis of the data from the 221 patients with bacterial endocarditis indicates that acute bacterial endocarditis and subacute bacterial endocarditis are two different entities which have a different pathogenesis and prognosis. It must be admitted that with antibiotic therapy currently available some patients with endocarditis caused by microorganisms of considerable virulence are kept

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leukemia in 2 patients. It cannot be assumed that an endocarditis which develops in a patient with disseminated lupus erythematosus is of the Libman-Sachs variety. A vigorous attempt must be made to rule out a bacterial component.

Laboratory findings. The most important laboratory procedure that was utilized in the diagnosis of acute bacterial endocarditis was the blood culture. Four patients had no blood for culture drawn, but necropsy disclosed acute bacterial endocarditis in every one. Blood cultures were positive during life in all but one of the other patients. This patient (Case 6) had sterile premortem blood cultures, but necropsy disclosed a bacterial endocarditis vegetation on a bicuspid aortic valve.

Eighty-two per cent of the patients whose blood was cultured had coagulase-positive staphylococci as an etiological agent. Coagulase-positive staphylococci were found in association with other microorganisms in 10 (24 per cent) of the 42 patients. However, the former was the predominant microorganism in all but one instance. In one patient, four other microorganisms were cultured. These were *Streptoccus faecalis*, *Echerichia coli*, Paracolobactrum, and *Candida albicans*. Two other microorganisms were cultured from 3 patients. These were *Pseudomonas aeruginosa* and *Candida albicans* in 2, and Proteus and coagulase-negative staphylococci in the other. One other species of bacteria was cultured from 6 patients. These were *Pseudomonas aeruginosa* in 3, and Proteus, *Streptococcus faecalis*, and alpha hemolytic streptococci in one each. Therefore, *Pseudomonas aeruginosa* was cultured from 5 (10 per cent) of the 50 patients.

Beta hemolytic streptococci and pneumococci were the etiological agents in 4 and 2 patients, respectively. Coagulase-negative staphylococci and alpha hemolytic streptococci were cultured from only 2 patients each and were the etiological agents of acute bacterial endocarditis in only one patient each.

Antibiotic susceptibility studies were infrequently made prior to 1955. Serum bactericidal levels were not determined during the period covered by this study.

Abnormal findings in the urine of patients with acute bacterial endocarditis were common: pyuria occurred in 90 per cent. Proteinuria and hematuria were also frequent; these occurred in 80 per cent of the patients. The average of the lowest recorded hemoglobin was 10.2 Gm. per cent; in 32 (61.5 per cent) of the 52 patients tested the lowest hemoglobin was less than 11 Gm. per cent. Ninety-six per cent of the patients had an elevated white blood cell count above 10,000 per cubic millimeter; in 55 per cent the count was greater than 20,000 per cubic millimeter. As would be expected, most of the leukocytes were polymorphonuclear. Histiocytes were specifically searched for in 7 patients and found in 2.

Erythrocyte sedimentation velocity (Westergren) was determined in only 25 of the 54 patients. In 22 (88 per cent) the erythrocyte sedimentation velocity was abnormally rapid. Blood urea nitrogen was abnormal in 34 (79 per cent) of the 43 patients tested. The serum albumin-globulin ratio was reversed in 22 of 26 patients, with the average total serum protein being 5.9 Gm. per cent. Obviously, both acute bacterial endocarditis and associated diseases, when present, contributed to the abnormal laboratory findings.

Electrocardiograms were obtained on 46 patients and were normal in 50 per cent. Eight patients had atrial fibrillation on admission to the hospital, and 2 more developed it.

A list of the seven most frequent abnormal physical and laboratory findings in the 54 patients is shown in Table II.

Table II. Summary of abnormal physical and laboratory findings in patients with acute bacterial endocarditis

Findings	*Per cent*	*Comment*
Positive blood culture	98	4 Not cultured
Fever and tachycardia	92.6	
Pyuria	90	4 No urinalysis
Murmur(s)	87	
Proteinuria	80	4 No urinalysis
Hematuria	78	4 No urinalysis
White blood cell count >15,000	73.6	1 Not determined

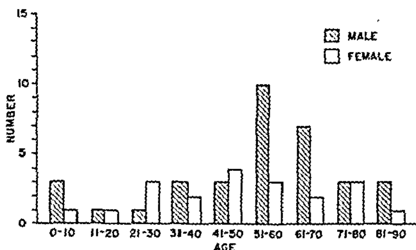


Fig. 1. Distribution of patients with acute bacterial endocarditis by age and sex.

alive and thereby reach the subacute stage. However, it was possible to establish an acceptable separation between the two forms by using the estimated date of onset. It is admittedly impossible to ascertain the exact date of onset in most instances.

Results

Age and sex. The distribution of patients by age and sex is shown in Fig. 1. The youngest patient was 15 days old at death and his case will be discussed later; the oldest patient was 84 years old. There were 34 males and 20 females. It is interesting that there were 4 patients who had acute bacterial endocarditis in the first decade of life. Thirty-two (59 per cent) were over 50 years old.

Underlying heart disease. Thirty-four (63 per cent) of the patients had no acquired valvular or congenital heart disease. In 4 of 5 patients who had underlying congenital heart disease a diagnosis of acute bacterial endocarditis was made in recent years (1956 and 1957). The remainder of the patients had underlying rheumatic heart disease.

Initiating factors. A possible predisposing factor that could have initiated the bacteremia which preceded the development of acute bacterial endocarditis was found for 31 (57 per cent) of the patients. Major and minor operations, such as extensive surgery for cancer and skin incisions for intravenous infusions (cut-downs), accounted for 71 per cent of the factors. Cystoscopy and/or urethral catheterization preceded the development of acute bacterial endocarditis in 4 male patients. Abortion was incriminated in 3 patients.

Symptoms. Symptoms which were related to other diseases with which the patient was afflicted often overshadowed those of acute bacterial endocarditis. Most of the patients developed acute bacterial endocarditis while being treated in the hospital for some other major illness.

Physical findings. The most prominent physical findings exhibited by the patients are shown in Table I. Fever and tachycardia occurred most frequently. Cardiac murmurs were heard in all but 7 patients. Physical findings were affected by associated cancer in 11 patients, disseminated lupus erythematosus in 2 patients, and

Table I. Physical findings in 54 patients with acute bacterial endocarditis

Findings	*Total*	*Per cent*
Fever and tachycardia	50	92.6
Murmur(s)	47	87.0
Cardiomegaly	26	48.1
Congestive heart failure	21	38.9
Positive neurological findings	21	38.9
Petechiae	19	35.2
Poor oral hygiene	14	25.9
Pallor	13	24.1
Splenomegaly	11	20.4
Jaundice	10	18.5
No murmur	7	13.0
Changing murmur	4	7.4

Table V. Location of abscesses found at autopsy in 28 patients with acute bacterial endocarditis

	Total	Per cent
Abscesses	28	100 0
Kidneys	18	64 3
Myocardium	17	60 7
Brain	13	46 4
Lungs	12	42 9
Spleen	8	28.6
Liver	7	25 0
Adrenals	3	10 7
Wound	3	10 7
Other	14	50 0

patients of similar age with subacute bacterial endocarditis, most of whom had underlying congenital or acquired valvular heart disease.[5]

The formation of abscesses occurred frequently and was thought to be due to septic emboli. Abscesses were found in the pancreas, parathyroid, colon, and small intestine, as well as at the more common sites listed in Table V.

Pneumonia and congestion of the lungs were both frequent. Infarcts of the spleen and kidneys occurred less frequently than in patients with subacute bacterial endocarditis.[5] As would be expected, the encephalitis, pericarditis, myocarditis, and meningitis were of the suppurative type. Septic coronary emboli occurred in 5 patients and caused acute myocardial infarction in one. The formation of a mycotic aneurysm occurred twice in the brain and was associated with hemorrhage both times.

Treatment. The patients in this series were treated with a variety of antibiotics, with greatly varying dosage. The only significant finding in an analysis of the treatment was that it was ineffectual in all but 2 of the patients. It should be pointed out that vancomycin was not used systematically in the treatment of staphylococcal endocarditis until after the period covered by this study. This antibiotic, as well as the staphylococcal penicillinase-stable penicillin, 2,6-dimethoxyphenyl penicillin (Staphcillin), appears to offer a better prognosis in the treatment of acute bacterial endocarditis due to penicillin-resistant coagulase-positive staphylococci.

Case reports

The cases of the 2 patients who survived are described briefly:

Case 1. A 44-year-old woman with mitral stenosis due to rheumatic heart disease developed fever after catheterization of the right side of the heart in 1952. Blood cultures grew beta hemolytic streptococci, and she was thought to have bacterial endocarditis. She responded well to penicillin and streptomycin therapy and subsequently had a successful mitral commissurotomy. She is presently doing well.

Case 2. A 36-year-old man with a history of acute rheumatic fever and a cardiac murmur was hospitalized with acute bacterial endocarditis in 1958. One month previously an infected tooth had fallen out. Physical examination revealed splenomegaly, purpura, and a loud murmur which was thought to represent mitral insufficiency. Blood cultures grew up to 400 colonies per milliliter of coagulase-positive staphylococci which were susceptible to 0.8 unit per milliliter of penicillin. He responded well to an intensive course of penicillin therapy.

Brief summaries of the cases of the 5 patients with underlying congenital heart disease follow:

Case 3. A 3-day-old infant was hospitalized in 1945, with a history of dyspnea and cyanosis when feeding. He developed impetiginous lesions on his legs, which were treated with penicillin, 2,500 units intramuscularly every 3 hours. Chest roentgenograms revealed an enlarged right ventricle, and he was thought to have congenital heart disease. White blood cell counts were over 20,000 per cubic millimeter on two occasions, with a predominance of polymorphonuclears. Blood cultures were not obtained. He died after 12 days of hospitalization, and at autopsy a patent foramen ovale, patent ductus arteriosus, hypertrophied right and left ventricles, and mural bacterial endocarditis with myocarditis were found. This patient was the youngest in this series, and, to the best of my knowledge, the youngest reported in the literature to have acute bacterial endocarditis.

In 1956, 2 patients with an interventricular septal defect developed acute bacterial endocarditis after cardiac surgery. The Ivalon patch used to close the defect was involved in both patients. Summaries of these 2 cases follow:

Case 4. Four days after operation, a 16-month-old male infant had coagulase-positive staphylococci cultured from an infected thoracotomy incision and from the blood, in up to 2,500 colonies per milliliter. The staphylococci were susceptible to 0.4 μg per milliliter of novobiocin, 1 5 μg per milliliter of erythromycin, and 3.1 μg per milliliter of vancomycin, chloramphenicol, and bacitracin. They were resistant to 100 units per milliliter of penicillin. Despite treatment with novobiocin, tetracycline, and chloramphenicol, the infant died 21 days later. At autopsy an acute bacterial endocarditis vegetation was found on the right ventricular side of the Ivalon graft which covered the interventricular fect; the vegetation extended up to the of the tricuspid valve and almost occl

Table III. Location of valvular lesions in patients who had acute bacterial endocarditis with no underlying heart disease

Valve(s) involved	*Males*	*Females*	*Total*	*Per cent*
Mitral	8	4	12	35 3
Aortic	2	4	6	17 7
Mitral and aortic	6	0	6	17 7
Tricuspid	3	2	5	14 7
Tricuspid and mitral	2	1	3	8 8
Tricuspid and aortic	1	0	1	2 9
Tricuspid, mitral, and aortic	1	0	1	2 9
Total	23	11	34	100 0

The erythrocyte sedimentation velocity was excluded from this list because less than half of the patients were tested.

Mortality. All but 2 of the 54 patients died in the hospital or within 3 months after discharge, which gives a 96.3 per cent mortality for acute bacterial endocarditis in this series.

Obviously, the diagnosis of acute bacterial endocarditis may have been missed in some patients who were cured of coagulase-positive staphylococcal "septicemia." If this factor could be analyzed, perhaps the "true" mortality would not be so high.

Necropsy findings. Necropsy was performed on 47 of the 51 patients who died in the University of Minnesota Hospitals. In addition, one patient who was treated at the University of Minnesota Hospitals died and underwent an autopsy in another Minneapolis hospital. Therefore, postmortem confirmation of the diagnosis was obtained in 48 (92 per cent) of the 52 patients who died.

Location of valvular lesions. The location of the valvular lesion(s) of acute bacterial endocarditis in patients with no underlying heart disease is shown in Table III. The mitral valve was most frequently involved; it was the location of a lesion of acute bacterial endocarditis in 22 (65 per cent) of the 34 patients. The most striking finding, however, was the relatively large number of patients with involvement of the tricuspid valve. In one patient the mitral, aortic, and tricuspid valves were involved. All four valves have been reported to be involved in staphylococcal endocarditis.[1]

The location of the valvular lesion(s) of acute bacterial endocarditis in patients with underlying rheumatic heart disease was similar to that found in patients with subacute bacterial endocarditis[4]: the mitral valve was most commonly affected. Necropsy confirmation of the involved valve(s) was obtained in all but 6 of the 49 patients described above. The 5 patients with underlying congenital heart disease will be discussed later.

Pathologic findings. The pathologic findings in the 48 patients are shown in Table IV. The pathologist was denied permission to examine the brain in 16 (33 per cent) of the 48 patients. Therefore, the percentages for the central nervous system are calculated using 32 as the total number of patients. An active endocardial lesion(s) was found in all patients. The average heart weight in patients over 10 years old was 439 grams (range, 250 to 650 grams) in males, and 322 grams (range, 255 to 470 grams) in females. These figures are approximately 100 grams lower than the average heart weight of male and female

Table IV. Autopsy findings in 48 patients with acute bacterial endocarditis

Findings	*Total*	*Per cent*
Active endocardial lesion(s)	48	100.0
Abscesses	28	58 3
Pneumonia	26	54.2
Encephalitis*	13	40.6
Congestion	19	39.6
Splenic infarct	16	33.3
Pericarditis	13	27.1
Myocarditis	11	22.9
Cancer	11	22.9
Renal infarct	11	22.9
Pyelonephritis	8	16 7
Embolic glomerulonephritis	7	14.6
Perforated valves	7	14.6
Coronary embolism	5	10.4
Subarachnoid and/or intracerebral hemorrhage*	3	9.4
Meningitis*	3	9.4
Mycotic aneurysm (noncerebral)	3	9.4
Mycotic aneurysm (cerebral)*	2	6.3

*Percentages calculated using as the total number (32) only the patients in whom an examination of the brain was performed.

review[1] in 1952 of recently reported cases revealed a ratio of streptococcal endocarditis to staphylococcal endocarditis of 2.6 to 1. At the University of Minnesota Hospitals the ratio of streptococcal (alpha hemolytic streptococci and *Streptococcus faecalis*) subacute bacterial endocarditis to staphylococcal acute bacterial endocarditis was 2.7 to 1 for the 21-year period. The ratio was 1.7 to 1 if only the last 5 years of the study were considered.

Forty-five per cent of the patients with acute bacterial endocarditis had the disease during the last 5 years of the study (1955-1959). The other 31 instances were evenly spread throughout the first 15 years. The rising incidence in recent years appears to be due to the increased frequency of vigorous diagnostic and operative procedures on elderly patients. Most of the patients in the present series were over 50 years of age, and the majority were males (Fig. 1). Possible predisposing causes of acute bacterial endocarditis, such as urethral catheterization, cystoscopy, and extensive surgery for cancer, were frequent in these patients In addition, decreased body defense mechanisms as a result of malnutrition, debilitation, and other diseases, are obviously important in increasing a patient's susceptibility to acute bacterial endocarditis.

Fever and tachycardia with murmur(s) were the most common physical signs (Table I). Although in 7 patients there was no record that murmurs were heard, perhaps a diligent search was not made, because at autopsy each one was found to have acute bacterial endocarditis On the other hand, MacGregor[6] reported on 3 patients with subacute bacterial endocarditis and one patient with acute bacterial endocarditis in whom no murmur was heard during the first part of the illness. Bacterial endocarditis should always be suspected in any patient with a fever of unknown origin, and blood for culturing should be obtained.

A positive blood culture was the most commonly occurring abnormal finding in patients with acute bacterial endocarditis (Table II). Coagulase-positive staphylococci were implicated as etiological agents of acute bacterial endocarditis in 82 per cent of the patients in the present series. This finding is similar to the experience reported by others.[1]

Infections caused by Pseudomonas are becoming more frequent and remain difficult to manage. There have been recent reports of Pseudomonas endocarditis after puerperal septicemia,[7] in a narcotic addict,[8] and associated with Pseudomonas endarteritis of a traumatic arteriovenous fistula.[9] Although Pseudomonas was considered to be the primary etiological agent in only one patient (Case 7) in the present series, it was cultured from the blood of a total of 5 patients during the course of their illness.

The recent literature has stressed that, although the incidence of bacterial endocarditis after cardiac surgery for congenital or acquired valvular heart disease is low,[10,11] the high mortality makes it imperative to consider this diagnosis as a possible cause of postoperative fever.[12-15] It is obvious from Cases 4, 5, and 7 that the Ivalon graft material used during cardiac surgery was at least one of the prime foci of infection, if not the main focus. It is remarkable that the foreign material used in cardiac surgery is not more frequently infected. The importance of not submitting postcardiac surgery patients to any procedure that may produce bacteremia needs to be stressed.

In addition to coagulase-positive staphylococci, Pseudomonas and Candida are being found more frequently to cause postcardiac surgery endocarditis.[16-18] One patient of this series (Case 7) had all 3 microorganisms cultured from his blood.

Acute bacterial endocarditis has been recognized as a disease which causes an extremely high mortality rate. In the present series of 54 patients, only 2 lived. Mortality rates of 74[19] and 87[20] per cent in cases of staphylococcal endocarditis have been reported. The difficulty in evaluating mortality rates in cases of bacterial endocarditis is enhanced by the fact that a patient with fever, a heart murmur, petechiae, and septicemia may not have an endocardial lesion. In the present study the diagnosis was confirmed at autopsy in 48 of the 52 patients who died.

Although no therapeutic recommendations can be made from this study, it appears from my personal experience that

Table III. Location of valvular lesions in patients who had acute bacterial endocarditis with no underlying heart disease

Valve(s) involved	Males	Females	Total	Per cent
Mitral	8	4	12	35.3
Aortic	2	4	6	17.7
Mitral and aortic	6	0	6	17.7
Tricuspid	3	2	5	14.7
Tricuspid and mitral	2	1	3	8.8
Tricuspid and aortic	1	0	1	2.9
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Total	23	11	34	100.0

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2,6-dimethoxyphenyl penicillin (8 to 20 grams per day) and/or vancomycin (3 to 6 grams per day) are the antibiotics of choice in the treatment of endocarditis due to penicillin-G-resistant staphylococci, and as part of the initial therapy in clinically diagnosed cases until the results of the blood cultures are known.

Prophylactic antibiotics should be given to all patients with rheumatic or congenital heart disease who undergo any diagnostic or operative procedure which involves incisions of the skin or manipulation of the mucous membranes. Briefly, it is recommended that an adult patient receive treatment 2 days before, the day of, and 2 days after the procedure. Procaine penicillin, 600,000 units,[21] or oral phenoxymethyl penicillin (Pen-V), 250 mg. (400,000 units), every 8 hours for each of the 5 days appears to be satisfactory for dental manipulations. For other procedures, such as catheterization *or surgery of the genitourinary tract, streptomycin, 1 Gm. a day, should* be added to the regimen of penicillin. Patients who are allergic to penicillin may be given erythromycin, 250 mg. four times daily, for prophylaxis in dental manipulations, and tetracycline, 1 Gm. a day, may be substituted for prophylaxis in genitourinary procedures.[21] For children, doses should be lowered according to age.

Summary

1. Fifty-four patients who had acute bacterial endocarditis were observed at the University of Minnesota Hospitals during 1939 through 1959; 45 per cent of the cases occurred after 1954. The disease is defined as a bacterial infection of the endocardium (valvular and/or mural) which gives rise to symptoms which last less than 50 days, associated for the most part with an invasive microorganism, and having a *fulminant* clinical course.

2. There were 34 males and 20 females, whose ages at death ranged from 15 days to 84 years. Fifty-nine per cent were over 50 years old; reasons for this fact included associated debilitating diseases and the more common use of diagnostic and/or operative procedures, such as urethral catheterization, cystoscopy, and extensive surgery for cancer, in the older aged group.

3. The most frequent abnormal physical and laboratory findings were: (a) positive blood culture (98 per cent) (most commonly, coagulase-positive staphylococci); (b) fever and tachycardia (93 per cent); (c) pyuria (90 per cent); (d) murmur(s) (87 per cent); (e) proteinuria (80 per cent); (f) hematuria (78 per cent); and (g) white blood cell count greater than 15,000 (74 per cent).

4. Fifteen patients had rheumatic heart disease, and 5 had congenital heart disease, but in the other 34 patients (63 per cent) no underlying congenital or acquired valvular heart disease was found.

5. All but 2 of the patients died in the hospital or within 3 months after discharge, which gives a mortality of 96 per cent. An autopsy was performed on 48 of the 52 patients. An active endocardial lesion was found in all patients and was often associated with the formation of abscesses, pneumonia, and congestive heart failure.

6. The importance of antibiotic prophylaxis in the prevention of bacterial endocarditis is stressed.

This investigation was carried out under the supervision and guidance of Dr. Wesley W. Spink.

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ings. The patients in this group had a clinical diagnosis of predominant mitral stenosis (which was substantiated by catheterization data). Twenty-three patients were operated on by the same experienced surgeon; the cross-sectional area of his index finger was measured and was found to be 1.3 square centimeters. The surgeon estimated the area of the valve by palpation and determined the presence of regurgitation with his gloved index finger. The evaluation of regurgitation depended on the estimated size of the valve opening as well as the force and the distance at which the regurgitant jet could be felt. The regurgitant volume was assessed as 1-plus through 4-plus. At operation, 11 of the 25 patients had pure mitral stenosis with a valve area which ranged from 0.5 to 1.5 cm.^{2}. The other 14 patients had moderate mitral stenosis with a valve area which ranged from 1 to 2 cm.^{2}. Of these 14 patients, 4 were considered to have 1-plus regurgitation, 7 had 2-plus regurgitation, and 3 had predominant mitral insufficiency with 3-plus regurgitation. The second group consisted of the other 25 patients who for various reasons were not operated on (Table I). All 50 patients were included in the assessment of morbidity associated with left atrial puncture, and correlation of left atrial pressures with pulmonary arterial wedge pressure.

Methods

All catheterizations, with two exceptions, consisted of catheterization of the right side of the heart and left atrial puncture, which was performed by the method of Bjork as modified by Fisher.[1-3] In 2 patients, only left atrial puncture was performed.

The patients were in the postabsorptive state and were premedicated with secobarbital alone or in combination with meperidine. Pressures were recorded on a Sanborn Poly-Viso, direct-writing, four-channel recorder, employing Statham 23Db strain-gauge transducers. The zero reference level for both pulmonary arterial wedge pressures and the left atrial pressure was 10 cm. above the level of the table. Continuous pressures were recorded as the PE50* polyethylene catheter was withdrawn from the left ventricle into the left atrium. For the determination of the atrioventricular diastolic filling gradient the left atrial and left ventricular pressure curves were superimposed as closely as possible in the same phase of respiration. In each case, at least two respiratory cycles were recorded and measured. The pressure tracing obtained through the PE50 catheter was slightly damped as compared to that obtained directly through the needle. The difference between the two recordings was so negligible that for practical purposes these tracings might be considered to be identical. The frequency response of the hydraulic system of the No. 7 catheter used for catheterization of the right side of the heart and that of the 18-gauge needle used for left atrial puncture were very similar. The individual left atrial waves were measured and analyzed according to their relative height and for the duration of the y descent. The mean left atrial pressures were determined by planimetry. The same measurements were made on pulmonary arterial wedge tracings.

Pulmonary arterial wedge pressures were recorded according to the criteria of Rapaport and Dexter.[7] The mean pulmonary arterial wedge pressure was compared with the mean left atrial pressure. The v waves in both left atrial and pulmonary arterial wedge pressures were analyzed and correlated.

The terminology of MacKenzie and Wiggers[4-6] was used in describing the atrial waves, which are both positive and negative. Of the positive waves, the a wave is caused by atrial systole, the c wave is due to closure of the atrioventricular valves, and the v wave is related to atrial filling. Two negative troughs are also described: the x wave, which follows the c wave, is caused by a drop in atrial pressure as the ventricles contract, and the y descent, which follows the peak of the v wave and ends in the y point, is due to lowering of the atrial pressure as the blood flows into the ventricles during diastole.

Results

Technical difficulties. The left atrium could not be entered in 5 patients; in 2 of these there was pericardial effusion which had not been detected on the chest x-ray

*Available from Clay-Adams, Inc., New York, N. Y. Inside diameter 0.023" and outside diameter 0.038".

Left atrial puncture in patients with rheumatic mitral valvular disease

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In spite of the advances made in surgical techniques, the correction of mitral regurgitation remains a difficult problem and is not entirely satisfactory. For this reason, careful judgment is required for correct selection of patients with combined mitral disease for surgical treatment.

The diagnostic difficulty in determining the predominant mitral lesion is considerable. It was hoped that the addition of left atrial puncture to our diagnostic armamentarium would greatly facilitate the differentiation of mitral regurgitation from mitral stenosis. Review of the literature disclosed, however, conflicting reports as to the value of left atrial puncture in general, and the analysis of left atrial curves in particular, in the diagnosis of predominant mitral valvular disease. The present study was undertaken in order to clarify the conflicting views and to assess the value of left atrial puncture in the diagnosis of lesions of the mitral valve. The investigation consists of three parts. The first part evaluates the results obtained from analysis of left atrial pressures as compared with surgical findings; the second part deals with the morbidity connected with left atrial puncture; and the third part tests the validity of pulmonary arterial wedge pressure as an indicator of left atrial pressure.

Material

The material for this investigation consisted of 50 patients who underwent a total of 52 left atrial punctures. The patients were divided into two groups (Table I). The first group consisted of 25 patients and forms the basis for analysis and correlation of atrial pressure curves with surgical find-

Table I

Group I: Patients operated on
- 11 patients—Pure mitral stenosis
- 4 patients—Mitral stenosis and Grade 1 mitral regurgitation
- 7 patients—Mitral stenosis and Grade 2 mitral regurgitation
- 3 patients—Minimal mitral stenosis and Grade 3 mitral regurgitation

Group II: Patients not operated on
- 12 patients—Minimal mitral stenosis and predominant mitral regurgitation
- 7 patients—Predominant mitral stenosis
- 2 patients—Aortic involvement
- 4 patients—No diagnosis

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Table II. Morbidity in 50 patients

	Number	*Per cent*
Pericardial tamponade	1	2
Pulmonary hemorrhage	1	2
Pneumothorax	2	4
Pulmonary infarction and fever	1	2
Postcommissurotomy-like syndrome	2	4
Asystole	1	2
Pleuritic pain	50	100
Signs of blood in pericardium at surgery	21	

missurotomy syndrome; the pain abated after a few doses of aspirin. One patient had a period of asystole which lasted 5 seconds as the needle punctured the left atrial wall. Most patients complained of pleuritic-type pain at some time during the 24 hours after the procedure. The pulmonary artery, aorta, right atrium, and right ventricle were sometimes inadvertently entered during attempts to puncture the left atrium. Fortunately, no untoward results occurred from the puncture of these structures. A small quantity of dark blood was found in the pericardium of 21 patients who underwent mitral commissurotomy shortly after the left atrial puncture.

Analysis of curves in the assessment of predominant valvular disease. We analyzed the characteristic left atrial waves in the tracings of 25 patients who underwent surgery. The most commonly used hemodynamic formulas which have been developed by various investigators to help separate mitral stenosis from mitral regurgitation were investigated and their value was assessed. These formulas are based on the relative height of the *v* wave and the rapidity of *y descent*, and are as follows: (1) rate of *y* descent during the first 0.1 second[8,9]; (2) height of *v* wave minus the height of *c* wave[2]; (3) the ratio of the height of *v* wave to the height of mean left atrial pressure[10]; (4) height of *v* wave minus mean left atrial pressure[11]; (5) absence of diastasis in mitral stenosis.[9] In addition to the afore-mentioned formulas, we developed in our laboratory, on the basis of the height and area of the *v* wave, two indices of mitral regurgitation. They consist of two formulas:

(1) (*v (height) − y*) × (*v (area) from x to x + 0.2 second*)
(2) (*v (height) − x*) × (*v (area) from x to x + 0.2 second*)

Of the criteria tested and previously reported to be valuable in the differentiation of mitral stenosis from mitral regurgitation, none adequately separated the two conditions. Fig. 1 shows graphically the random distribution of points when results analyzed according to each of the formulas mentioned above were plotted against our estimate at the time of operation.

According to Braunwald, diastasis is absent in mitral stenosis. Diastasis is the rise in left atrial pressure just before onset of the *ac* wave. It is due to a rise in ventricular pressure as the ventricle is filled with blood.[9] Of the 25 cases evaluated at the time of operation, diastasis was present in 5. Two patients had predominant mitral stenosis with Grade I and II regurgitation, and 3 patients had pure mitral stenosis.

In the other 20 patients, diastasis was not demonstrable. Among these there were 8 cases of pure mitral stenosis, 3 cases of moderate mitral stenosis with Grade I regurgitation, 6 cases of Grade II regurgitation, and 3 cases of predominant mitral regurgitation (Grade III regurgitation). From this analysis, we concluded that absence of diastasis in our cases was not a

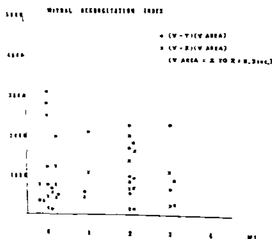


Fig. 2. The values derived from the application of the mitral regurgitation index to left atrial pressure curves are plotted as ordinates. The degree of mitral regurgitation (0-4) is plotted as abscissas. Note the failure to separate mitral regurgitation from mitral stenosis.

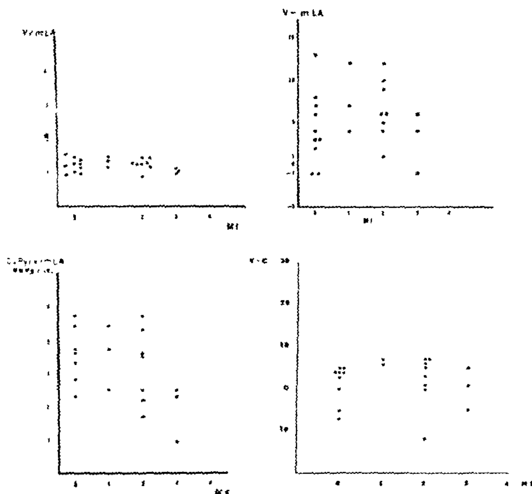


Fig. 1. Relationship between values derived from analysis of left atrial pressures and the degree of mitral regurgitation. The values obtained from the application of four formulas (*see text*) are plotted as ordinates, and the degree of mitral regurgitation (0-4) is plotted as abscissas. Note the failure to separate mitral stenosis from mitral regurgitation.

film. In the other 47 successful left atrial punctures, the PE50 catheter failed to enter the left ventricle in 10 patients. In 6 patients the "washout" phenomenon was encountered: the polyethylene tubing was washed back from the left ventricle into the left atrium by the regurgitant stream of blood during ventricular systole. In no case did knotting or accidental cutting of the PE50 polyethylene catheter occur.

Morbidity. Short periods of arrhythmia (consisting predominantly of premature ventricular beats and changes in rhythm) were encountered in about 60 per cent of the patients as the needle entered the left atrium. Discomfort in the form of pain was experienced by most patients. The over-all morbidity was significant, but no permanent disability or death resulted from the 52 left atrial punctures.

The salient features of these complications are summarized in Table II. Pericardial tamponade occurred in one patient several hours after the procedure. The patient responded well to pericardiocentesis and recovered. Another patient had a pulmonary hemorrhage immediately after the removal of the intracardiac needle; this was due to puncture of lung parenchyma. Two patients developed small pneumothoraces. Another patient developed fever and signs of infiltration in the left lung, which were probably due to emboli that originated in the right atrium, which was inadvertently punctured. Two patients had severe precordial pain which resembled the postcom-

tral regurgitation was ventricularization of the left atrial pressure curve (Fig. 4), indicating a common atrioventricular chamber.

The mean atrioventricular gradient was determined in 19 of the 25 patients in Group I. For 7 patients with pure mitral stenosis it averaged 9.3 mm. Hg. For 6 patients with mitral stenosis and Grade 2 mitral insufficiency it averaged 10.6 mm. Hg. In one patient with Grade 3 mitral insufficiency it was 9 mm. Hg. It is obvious that, although the gradient indicates the presence of some mitral stenosis, it does not help to differentiate pure mitral stenosis from mitral stenosis with significant mitral insufficiency.

Correlation of left atrial pressure with pulmonary arterial wedge pressure. Correlation of pulmonary arterial wedge pressure with left atrial pressure was possible in 37 patients. In 12 patients the pulmonary arterial wedge pressure was nonphasic or damped, which made the identification of individual waves impossible. In the other 25 patients the individual waves were well recorded and could be compared with characteristic left atrial pressure waves. Good correlation was obtained in the comparison of pulmonary arterial wedge pressure with left atrial pressure (Fig. 5). The correlation coefficient for the mean left atrial and mean pulmonary arterial wedge pressure was $r = +0.68$. A somewhat better figure of $r = +0.72$ was obtained for the correlation of the *v* waves. The coefficient of regression was 0.78.

These results corroborate the findings of other investigators that pulmonary arterial wedge pressure is a good indicator of left atrial pressure, not only in terms of mean pressure but also in terms of individual waves.[15-22] In the 25 patients in whom the pulmonary arterial wedge pressure disclosed phasic variations, the mean left atrial pressure varied between 11 and 34 mm. Hg. The height of left atrial pressure, therefore, did not seem to influence the transmission of individual waves from the left atrium to the catheter wedged in a branch of the pulmonary artery.

Discussion

When the technique of left atrial puncture was introduced, it was hoped that it would be helpful in differentiating mitral regurgitation from mitral stenosis in combined mitral lesions. In our series of 50 patients, left atrial puncture was associated with considerable morbidity, and the analysis of left atrial pressures has not consistently separated mitral stenosis from mitral regurgitation. The various hemodynamic formulas proposed for the detection of mitral regurgitation were not helpful in this study. Similar negative findings have also been reported by other investigators.[21-26] The reasons for this are not en-

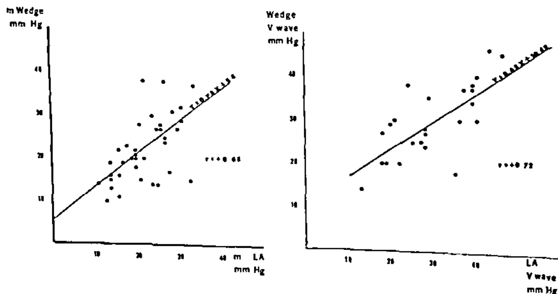


Fig. 5. Relationship between left atrial and pulmonary arterial wedge pressures. Note the close correlation between mean pressures and *v* waves.

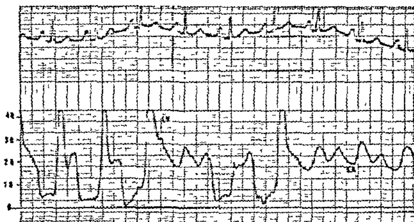


Fig. 3. The "washout phenomenon" The plastic catheter is washed from the left ventricle back into the left atrium during ventricular systole.

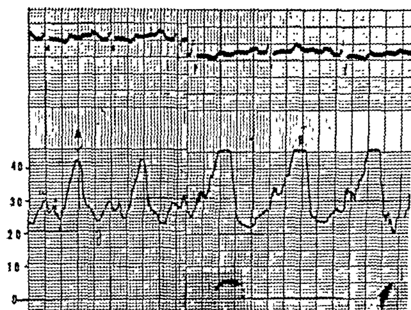


Fig. 4. Ventricularization of left atrial pressure. *A* shows preoperative left atrial curve *B* shows the same pressure after mitral commissurotomy which resulted in severe mitral regurgitation

reliable criterion for the diagnosis of mitral stenosis.

Examination of Fig. 1 discloses the lack of separation between predominant mitral stenosis and mitral regurgitation. None of the formulas tested separated the two conditions satisfactorily. The index of mitral regurgitation suggested by us (Fig. 2) likewise failed to separate the two conditions. Although the hemodynamic criteria derived from the analysis of left atrial pressure curves proved to be disappointing, two phenomena seemed to indicate predominant mitral regurgitation. One which has been reported previously[12-14] is the catheter "washout," in which event the small polyethylene catheter enters the left ventricle in diastole but is immediately washed back into the left atrium by the regurgitant flow of blood during ventricular systole (Fig. 3). We observed this phenomenon in all 3 patients who were found at operation to have predominant mitral regurgitation. The second persistent finding in predominant mi-

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tirely clear. One possibility is that we measure only the relative height of the different atrial waves, without taking into consideration the pressure-volume relationship in the atrium and the elasticity of the left atrial wall.[8,26,27] The other possibility is that the assessment of regurgitation by the surgeon is not reliable The finger in the left atrium may distort the valvular ring and cause a false impression of regurgitation.

Left atrial puncture is reliable in the diagnosis of significant mitral stenosis or pure mitral regurgitation. However, such a diagnosis may also be established with a high degree of accuracy by clinical methods alone. There are two groups of patients in whom left atrial puncture is indicated. One group of patients consists of so-called silent mitrals. These patients have all the symptoms of mitral stenosis but lack the characteristic murmur. The demonstration of a significant atrioventricular gradient across the mitral valve by means of left atrial puncture is of prime importance. The second group consists of patients with congestive heart failure and an enlarged left atrium without other diagnostic features. Catheterization of the right side of the heart usually demonstrates a high pulmonary arterial wedge pressure and a high right ventricular end-diastolic pressure. Left atrial puncture will help to rule out mitral stenosis by the absence or presence of an atrioventricular gradient.

In view of the relatively high morbidity associated with this procedure and the unreliable data obtained from the analysis of atrial curves, this procedure should not be undertaken lightly. This impression is further strengthened by the fact that a good correlation was obtained from the comparison of left atrial pressure with pulmonary arterial wedge pressure. On the basis of our findings, a properly recorded pulmonary arterial wedge pressure, both at rest and during exercise, provided sufficient diagnostic information.

The presence of an atrioventricular gradient is sometimes misleading, because a large gradient may also exist in patients with combined mitral lesions with significant mitral regurgitation. Atrioventricular gradients should, however, be determined during mitral commissurotomy, before and after the opening of the mitral valve. Abolition of the atrioventricular gradient affords a quantitative measure of the successful relief of mitral stenosis.

Mitral regurgitation may be best assessed by actual measurement of the volume of the regurgitant flow of blood. Recent advances in retrograde angiocardiography indicate that this may be the best method in the future.[28,29] It is proposed that, within the present means of analysis, left atrial puncture affords few advantages in most cases, and emphasis should be placed on clinical evaluation of the patient, combined if necessary with catheterization of the right side of the heart.

Summary

The value of percutaneous transthoracic left atrial puncture in the diagnosis of predominant mitral regurgitation was studied in 50 patients with combined lesions of the mitral valve. The investigation was divided into three parts and consisted of: (1) assessment of morbidity associated with this procedure, (2) comparison of surgical findings with the results of analysis of left atrial pressure curves, and (3) correlation of left atrial pressure curves with the pulmonary arterial wedge pressure-pulse contours.

The results obtained indicate that percutaneous transthoracic left atrial puncture was associated with significant morbidity. The analysis of left atrial pressure curves did not consistently separate mitral regurgitation from mitral stenosis. Pulmonary arterial wedge pressure, on the other hand, correlated well with the left atrial pressure curves.

The results of this investigation are discussed and indicate that left atrial puncture in most cases of combined mitral lesions affords few advantages. For this reason, emphasis should be placed on clinical evaluation of patients, combined, if necessary, with catheterization of the right side of the heart.

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Table I. Data on the TsÊ loop of 23 patients with ostium secundum type of atrial septal defect

Patient	Age, Sex	*Maximal T vector*			*T loop (l/w ratio)*	*QRS-T angle (degrees)*		*Pulmonary arterial pressure (mm Hg)*	*PBF/SBF*
		Angle (degrees)		*Magnitude (mv.) (Front.)*					
		Front.	*Sag.*			*Front.*	*Sag.*		
1.	29, M	+ 47	+126	0 159	2.7	98	40	Mild hypertension	—
2.	41, F	− 12	−100	0 224	1 8	120	180	31	4 5
3.	42, F	− 10	− 82	0 171	1 1	120	163	—	—
4.	4.5, M	0	+ 20	0 211	1 5	123	60	—	—
5.	32, F	+ 52	+ 35	0 101	0 7	95	73	Normal	—
6.	27, F	+ 50	+125	0 146	3 0	37	32	—	—
7.	26, F	+ 66	+120	0 203	2 5	33	15	44	2 0
8.	46, M	+ 78	+151	0 106	4 6	17	8	Severe hypertension	—
9.	19, F	+ 12	+158	—	—	142/43*	30	45	2 5
10.	32, F	− 95	− 5	0 337	4 3	160	193	38	7 5
11.	35, F	− 65	− 52	0 211	0 9	170	165	45	2 2
12.	16, F	+ 78	+ 55	0 062	2 1	60	35	—	—
13.	28, M	− 9	− 11	0 191	4 9	149/22*	113/44*	66	1 6
14.	13, F	+ 13	+164	0 149	10 5	153	169	—	—
15	9.5, F	+ 21	+ 33	0 223	4 9	17	2	—	—
16.	10, M	+ 47	+ 68	0 648	4 1	53	47	20	2 0
17.	35, F	+ 58	+105	—	—	59	25	30	2 2
18.	16, F	+ 62	+145	0 189	6 3	37	25	40	2 2
19.	10, M	+ 50	+105	0 380	15 2	15	29	Normal	—
20.	15, F	− 40	− 10	0 154	1 9	170/25*	173/7*	—	—
21.	7, F	− 62	− 36	0 183	1 9	163	164	40	4 0
22.	33, F	+114	+ 78	0 161	2 5	9	30	—	—
23.	— M	− 55	− 45	0 266	3 3	177	170	40	3 4

*When two values are given, the first number represents the value of the angle between the maximal mean instantaneous vectors of that portion of the QRS loop to the right of the isopotential point (terminal part of the QRSsÊ loop) and the TsÊ loop, and the second number represents the angle between the maximal mean instantaneous vectors of that portion of the QRS loop to the left of the isopotential point (initial part of the QRSsÊ loop) and the TsÊ loop.
Front.: Frontal plane projection. Sag.: Left sagittal plane projection. QRS-T angle: The angle between the maximal mean instantaneous vector of the QRS and TsÊ loops. PBF: Pulmonary blood flow. SBF: Systemic blood flow.

mean instantaneous vectors of the TsÊ loops. They varied in direction in the frontal plane projection from −95 to +114 degrees, and in the left sagittal plane projection from −100 to +164 degrees (Table II). The maximal vectors of the TsÊ loop in the patients with the most marked right ventricular hypertrophy were located in the sextants of negative values (Fig. 2).

ANGLE BETWEEN MAXIMAL MEAN INSTANTANEOUS VECTORS OF QRS AND TsÊ LOOPS. From the magnitude of this angle it is evident that all patients could be divided into two subgroups. One subgroup included patients with angles between +9 and +60 degrees in the frontal plane projection, and between +4 and +47 degrees in the left sagittal plane projection. These patients had little right ventricular hypertrophy, or only hypertrophy of the crista supraventricularis. The patients whose vectorcardiograms showed wide angles, which ranged from +149 to +177 degrees in the frontal plane projection and from +154 to +193 degrees in the left sagittal plane projection, had marked right ventricular hypertrophy. The magnitude of the angles of the spatial vectorcardiograms of the other patients varied between these two subgroups.

From data obtained at cardiac catheterization for one half of the patients, a direct relationship was found between the magnitude of the pulmonary blood flow and the magnitude of this angle, rather than between pulmonary arterial pressure and the magnitude of this angle. Well-developed features of right ventricular hypertrophy

The TsÊ loop in congenital atrial septal defect and persistent atrioventricular canal

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The value of conventional electrocardiography (ECG) and spatial vectorcardiography (sVCG) in the differential diagnosis of the secundum and primum types of congenital atrial septal defect is well known.[1-14] It has been shown that there is usually no relationship between the degree of hemodynamic disturbance and the magnitude of the changes in the electrocardiogram and vectorcardiogram.[6,9-10,12,14] The rate and nature of the changes toward normal after operation have also been studied.[15] The mechanisms for the marked left axis deviation in association with the primum type of defect still remain unknown.[14,17]

Most of the vectorcardiographic studies have been concerned primarily with the QRSsÊ loop, and little attention has been given to the changes in the TsÊ loop. This study is concerned with the TsÊ loop and its relation to the QRSsÊ loop in patients with atrial septal defects.

Material and methods

This report is based on a study of the spatial vectorcardiograms of 23 patients with ostium secundum defects and 7 patients with ostium primum defects in whom the recorded TsÊ loop was satisfactory for analysis. The diagnosis was established by cardiac catheterization, operation, or autopsy.[7,11,18] The equilateral tetrahedral reference system was used in recording the spatial vectorcardiograms.[19] Most of these patients were the same as those included in a previous analysis of the QRSsÊ loop.[11]

The ages of the patients with ostium secundum defects ranged from 4.5 to 46 years; 7 of these patients were males and 16 were females. The ages of the patients with ostium primum defects ranged from 5 months to 62 years, and all of these patients were females.

All measurements were obtained for the frontal and left sagittal plane projections, except the measurements of the magnitude of the maximal mean instantaneous vectors of the TsÊ loops and sJ, which were for the frontal plane only.

Results

Ostium secundum defect.

Fig. 1 illustrates the configuration in the frontal and left sagittal plane projections of the spatial vectorcardiograms of the 23 patients with ostium secundum defects.

SPATIAL ORIENTATION OF TsÊ LOOP. Figs. 2 and 3 and Table I summarize the magnitude and spatial orientation of the maximal

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frontal and left sagittal plane projections. The rotation was usually clockwise in the frontal plane projection and counterclockwise in the left sagittal plane projection of normal subjects.[18]

THE sJ VECTOR. The magnitude and spatial orientation of the sJ vector are shown in Tables II and IV and Fig. 3. The sJ vectors were directed superiorly, and the average magnitude of these vectors greatly exceeded that found in normal subjects. Despite the same high amplification used for most of the recordings, the sJ vector was measurable only in the vectorcardiograms with "circular" TsÊ loops (low l/w ratio). The patients had marked right ventricular hypertrophy.

Table IV. The magnitude and spatial orientation of the sJ vector in ostium secundum type of atrial septal defect

Patient	Angle (degrees)		Magnitude (mv.) (Frontal)
	Frontal	Left sagittal	
1.	− 12	—	0 031
2	− 75	−100	0 077
3	− 85	− 90	0 059
4.	− 63	—	0 064
11	−116	− 60	0 114
17.	− 75	− 82	—
22.	−105	− 68	0 095
23.	− 68	− 51	0 141

Ostium primum defect.

The frontal and left sagittal plane projections of the spatial vectorcardiograms of the 7 patients with atrial septal defect of the ostium primum type (including persistent atrioventricular canal) are shown diagrammatically in Fig. 4.

SPATIAL ORIENTATION OF TsÊ LOOP. As described previously,[11-14] the typical feature of the vectorcardiogram is the location of the QRSsÊ loop in space above the isopotential point, with its maximal mean instantaneous vector oriented upward and to the left or right. The TsÊ loop has been found to be oriented essentially 180 degrees away from the QRSsÊ loop.[11,12,14]

The spatial orientation of the TsÊ loop in the 7 patients reported on here is summarized in Fig. 2. The range in direction of the maximal mean instantaneous vector was from +10 to +123 degrees in the frontal plane projection, and from 0 to +112 degrees in the left sagittal plane projection. The magnitude and spatial orientation of this maximal vector are summarized in Table V.

The maximal mean instantaneous vectors of the QRSsÊ loop tended to vary little in spatial orientation in comparison to those of the TsÊ loops. The TsÊ loops tended to shift to the right and anteriorly in the patients with marked left ventricular

*Table V. Data on the TsÊ loop of 7 patients with ostium primum type of atrial septal defect**

Patient	Age, Sex	Maximal T vector			T loop (l/w ratio)	QRS-T angle (degrees)		Remarks
		Angle (degrees)		Magnitude (mv.) (Front.)				
		Front.	Sag.			Front.	Sag.	
1.	29. F	+ 92	+ 92	0 114	2 0	155	158	Left ventricular hypertrophy
2.	62. F	+ 54	+110	0 102	2 9	164/15	172	
3	5. F	+ 22	+ 42	0 313	1 7	135/64	108	
4.	42. F	+ 10	+103	0 282	4 5	125/58	10/172	Left ventricular hypertrophy and left bundle-branch block
5	5 mo., F	+123	+112	0 347	1 8	154	166	Left ventricular hypertrophy
6.	18. F	+ 26	0	0 407	2 8	110/73	75/115	
7.	8. F	+ 10	+ 53	0.308	1 8	53	173/118	Hypertrophy of crista supraventricularis

*See footnotes to Table I.

*Table II. Comparison of data on the TsÊ loop and sJ vector in patients with ostium secundum and ostium primum type of atrial septal defects**

Range and mean	Maximal T vector: Angle (degrees) Front	Maximal T vector: Angle (degrees) Sag	Maximal T vector: Magnitude (mv.) (Front)	T loop (l/w ratio)	QRS-T angle (degrees) Front.	QRS-T angle (degrees) Sag.	sJ vector: Angle (degrees) Front.	sJ vector: Angle (degrees) Sag.	sJ vector: Magnitude (mv.) (Front.)
A. Ostium secundum type									
Minimum	− 95	−100	0.062	0.7	9	2	− 12	− 51	0.031
Maximum	+114	+164	0.648	15.2	177	180	−116	−100	0.141
Average	+ 30	+ 53	0.213	3.85	95	84	− 75	− 75	0.083
B. Ostium primum type									
Minimum	+ 10	0	0.102	1.7	54/73	108/172	−123	− 52	0.070
Maximum	+123	+112	0.407	4.6	110/164	10/75	+170	+170	0.256
Average	+ 48	+ 73	0.266	2.5	—	—	—	—	—

*See footnotes to Table I.

Table III. Ostium secundum type of atrial septal defect

Plane projection	Direction of inscription of the TsÊ loop: +	−	+−	−+	?	Total
Frontal	11	−	2	—	10	23
Left sagittal	8	1	1	—	13	23

+, Clockwise rotation. −, Counterclockwise rotation. ?, Undetermined.

in the QRSsÊ loop were found in the patients in whom the ratio between pulmonary blood flow and systemic blood flow was greater than 3.0. All of these patients had large angles between the maximal mean instantaneous vectors of the QRS and TsÊ loops.

MAGNITUDE OF MAXIMAL MEAN INSTANTANEOUS VECTOR OF TsÊ LOOP. The magnitude of the maximal mean instantaneous vector of the TsÊ loop is shown in Table I and Fig. 3. The values ranged from 0.062 to 0.648 mv. (mean, 0.213 mv.). There was no characteristic value for the type of TsÊ loop described below or the angle between the maximal mean instantaneous vectors of the QRS and TsÊ loops. In general, the average magnitude tended to be less than that for normal subjects, rarely exceeding 0.250 mv.

RATIO BETWEEN MAXIMAL LENGTH AND WIDTH OF TsÊ LOOP. The ratios of the maximal length to width (l/w) of the TsÊ loops are shown in Table I. When the l/w ratio of 3.5 was accepted as a borderline value between the normal and abnormal,[18] it was found that 13 of the 23 patients had values of less than 3.5. Nine of the 13 patients had moderate to marked right ventricular hypertrophy, with wide angles between the maximal mean instantaneous vectors of the QRS and TsÊ loops. The other 4 patients had electrocardiographic and spatial vectorcardiographic manifestations of either mild right ventricular hypertrophy or hypertrophy of the crista supraventricularis (Patients 6, 7, 12, and 22).

DIRECTION OF INSCRIPTION OF TsÊ LOOP. The directions of inscription of the TsÊ loops are shown in Table III. It was not possible to determine the direction of rotation in some instances. In almost all instances, where measured, the rotation of the TsÊ loop was clockwise in both the

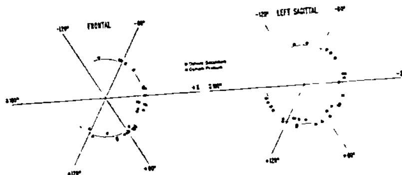


Fig. 2. Spatial orientation of maximal mean instantaneous vectors of the TsÊ loops in the patients with ostium primum, and in those with ostium secundum, types of atrial septal defect.

Table VI. Ostium primum type of atrial septal defect

Plane projection	Direction of inscription of the TsÊ loop					Total
	+	−	+−	−+	?	
Frontal	2	3	—	—	2	7
Left sagittal	1	3	—	—	3	7

+: Clockwise rotation −: Counterclockwise rotation ?: Undetermined

and that of the TsÊ loops varied from 110 to 164 degrees in the frontal plane projection. The angle between the maximal vector of the portion of the QRSsÊ loop to the left of the isopotential point and that of the TsÊ loop ranged from 15 to 73 degrees in the frontal plane projection.

In the patients with left ventricular hypertrophy, in whom there was no big portion of the QRSsÊ loop to the right of the isopotential point (Patients 1 and 5), the angle between the maximal mean instantaneous vectors of the main body of the QRSsÊ loop and the maximal vector of the TsÊ loop was large. The values of these angles were enclosed in the range found for the angles between the right portion of the QRSsÊ loop and the TsÊ loop of the patients with right ventricular hypertrophy alone.

The magnitude of the above-defined angles varied from 108 to 172 degrees in the left sagittal plane projection. In only a few spatial vectorcardiograms was the portion of the QRSsÊ loop to the right of the isopotential point clearly distinguishable enough to permit satisfactory measurements. In these spatial vectorcardiograms the angles were much smaller, ranging from 10 to 75 degrees. The angles in the left sagittal plane projection appeared, therefore, to have little value in the differentiation between left ventricular hypertrophy and right ventricular hypertrophy.

Magnitude of maximal mean instantaneous vector of TsÊ loop. The values for all patients are shown in Table V and Fig. 5. The magnitude of the maximal mean instantaneous vectors of the TsÊ loop varied from 0.102 to 0.407 mv. (mean, 0.266 mv.) (Table II). The mean values for this vector were slightly greater than the values for the vectors of patients with the

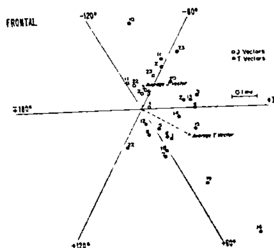


Fig. 3. The spatial orientation and magnitude of the maximal mean instantaneous vectors of the TsÊ loops and of the sJ vectors for the patients with the ostium secundum type of atrial septal defect. Average values for both vectors are shown.

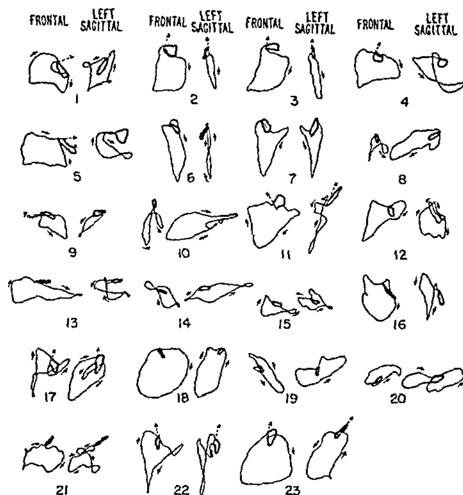


Fig. 1. Diagrams of spatial vectorcardiograms of the 23 patients with the ostium secundum type of atrial septal defect. These diagrams are not drawn to scale. They only show the configuration and spatial orientation.

hypertrophy (Patients 1 and 5) or combined left and right ventricular hypertrophy. This feature may be of diagnostic significance in the evaluation of left ventricular hypertrophy in association with right ventricular hypertrophy.

ANGLE BETWEEN MAXIMAL MEAN INSTANTANEOUS VECTORS OF QRS AND TsÊ LOOPS. The data for these angles are presented in Table V. In most of the patients the QRSsÊ loop had large terminal mean instantaneous vectors which were directed to the right and anteriorly. In these instances the angle was measured between the maximal mean instantaneous vectors of both portions of the QRSsÊ loops and the maximal vector of the TsÊ loop. It can be seen that large angles existed in the frontal plane projections between the maximal mean instantaneous vectors of the terminal portion of the QRSsÊ loop and the maximal vector of the TsÊ loop in the patients with right ventricular hypertrophy (Table V). In the patients with left ventricular hypertrophy (Patients 1 and 5), large angles were found between the maximal vector of the QRSsÊ loop to the left of the isopotential point (ip) or its main portion and the maximal vector of the TsÊ loop (Table V). This feature in addition to the spatial orientation of the TsÊ loop may also be helpful in differentiating between the patients with left ventricular hypertrophy and those with right ventricular hypertrophy.

The range of the magnitude of the angle between the maximal mean instantaneous vector of the right portion of the QRSsÊ loops to the right of the isopotential point

cal features, however, which were dependent upon the presence of hypertrophy of the ventricles. The spatial orientation of the TsÊ loops in the patients with the ostium secundum type of defect overlapped the range of spatial distribution of the TsÊ loops in the patients with ostium primum defects (Fig. 2). When the spatial orientation of the TsÊ loops is compared with the magnitudes of the angles between the maximal mean instantaneous vectors of the QRS and TsÊ loops, data of clinical value may be obtained. For instance, patients with ostium secundum defects had TsÊ loops which were directed in the range found for the normal subjects. At times there were small angles between the maximal mean instantaneous vectors of the QRS and TsÊ loops, especially when the QRSsÊ loop was distorted relatively little. This angle was large when the whole body or big terminal portion of the QRSsÊ loops was markedly distorted because of right

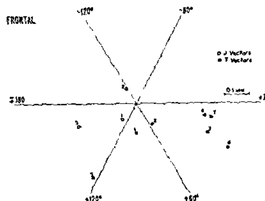


Fig. 5. Distribution and magnitude of the maximal mean instantaneous vectors of the TsÊ loops and of the sJ vectors for the patients with the ostium primum type of atrial septal defect.

ventricular hypertrophy. In the patients with the most marked right ventricular hypertrophy, in whom the QRSsÊ loop had two large mean instantaneous vectors, one for the portion to the left and the other to the right of the isopotential point, the TsÊ loop was found to be directed to the left, posteriorly, and above the horizontal plane. Simultaneously, large angles were found between the maximal vectors of the QRS and TsÊ loops.

The TsÊ loop in 5 of the 7 patients with ostium primum defect was directed to the left, posteriorly, and downward. The T and QRSsÊ loops were widely separated. The angles which the maximal vector of the TsÊ loop formed with that of the main body of the QRSsÊ loop were somewhat less than 90 degrees in the frontal plane projection. The terminal portions (which were usually portions to the right of the isopotential point) of the QRSsÊ loops generally were not well developed. However, the TsÊ loops were always spatially oriented opposite in direction to these terminal portions of the QRSsÊ loops, displaying angular deviations between 110 and 164 degrees in the frontal plane projection. Two patients with left ventricular hypertrophy displayed this feature remarkably well, a feature shown to be characteristic of left ventricular hypertrophy due to acquired heart disease.[20]

The average magnitudes of the maximal mean instantaneous vectors of the TsÊ loops for the patients with ostium secundum defect were about 30 per cent smaller than for normal subjects, and only about 15 per cent smaller for the patients with ostium primum defect than that for normal subjects. There was no direct relationship between the type or degree of hypertrophy

Table VII. The magnitude and spatial orientation of the sJ vector in ostium primum type of atrial septal defect

Patient	Angle (degrees)		Magnitude (mv.) (Frontal)	Remarks
	Frontal	Left sagittal		
1.	+135	+100	0.089	Left ventricular hypertrophy
2.	−123	− 52	0.070	Right ventricular hypertrophy
5.	+170	+170	0.256	Left ventricular hypertrophy

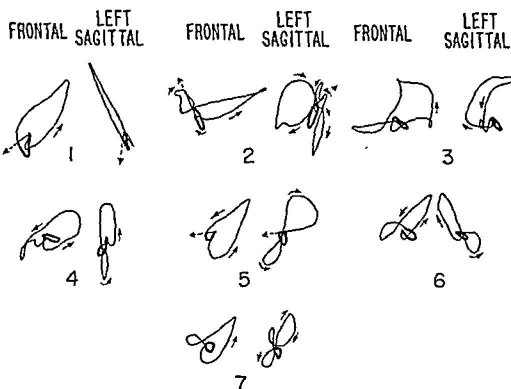


Fig. 4. Diagrams of spatial vectorcardiograms for the patients with the ostium primum type of atrial septal defect.

ostium secundum type of defect, but smaller than those found for the vectors of normal subjects.[18]

RATIO BETWEEN MAXIMAL LENGTH AND WIDTH OF TsÊ LOOP. The ratios of the maximal length and width (l/w) of the TsÊ loop for these 7 patients with ostium primum defects were some of the smallest found; the ratios were smaller than in any other group of patients with congenital heart disease studied thus far. The l/w ratios varied from 1.7 to 4.6; the mean was only 2.5. The mean was much lower than that accepted as the lower limit for normal subjects.[18]

DIRECTION OF INSCRIPTION OF TsÊ LOOP. The directions of rotation of the TsÊ loop are shown in Table VI. Because of the small number of patients studied and the difficulties involved in determining the direction of rotation in some TsÊ loops, it was not possible to know whether the pattern was typical. It appears that counterclockwise rotation is common for both the frontal and left sagittal plane projections.

THE sJ VECTOR. The sJ vector could be satisfactorily analyzed in only 3 of the 7 patients (Table VII; Fig. 5). Two of these patients had left ventricular hypertrophy. The sJ vectors were directed to the right, downward, and anteriorly in these 2 patients. The magnitude of the sJ vectors was greater than the average found for the patients with right ventricular hypertrophy among those with the ostium secundum type of defect. The sJ vector was directed essentially 180 degrees, opposite in spatial orientation from the maximal mean instantaneous vector of the QRSsÊ loop. The third patient had right ventricular hypertrophy only, and the sJ vector was the smallest of the three measured. It was also directed to the right, but was oriented posteriorly and above the isopotential point. It was spatially oriented, essentially like the maximal mean instantaneous vector of the terminal portion of the QRSsÊ loop.

Discussion

The QRSsÊ loops have been shown to be characteristically different and typical for both the secundum and primum types of atrial septal defect. The TsÊ loops were less characteristic. There were certain typi-

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of either of the ventricles in patients whose spatial vectorcardiograms showed high voltage of the TsÊ loop.

The shape of the TsÊ loop was expressed as a ratio between its maximal length and width. This ratio was rather low for the patients with the secundum type of defect, but the mean ratio was 3.85, and was greater than the lower limits of normal, 3.5. Thirteen of the 23 patients had a ratio below 3.5. The mean l/w ratio was 2.5 for the patients with ostium primum defects. In only one patient (ratio of 4.5) was the ratio greater than the lower limits of normal.

The magnitude of the sJ vectors in the spatial vectorcardiograms of the patients with ostium secundum defect which were satisfactory for study was much greater than that found in normal subjects, and was found in patients who had severe right ventricular hypertrophy. These vectors were directed superiorly. The sJ vectors in the patients with ostium primum defect were also extremely high in magnitude. They were oriented below the isopotential point in the patients with left ventricular hypertrophy. The sJ vectors in the patients with marked right ventricular hypertrophy were oriented above the isopotential point.

The direction of rotation of the TsÊ loop was mostly clockwise in both the frontal and left sagittal plane projections for the patients with ostium secundum defects. The direction of rotation of the TsÊ loops could not be adequately defined for the patients with ostium primum defects, since only 5 spatial vectorcardiograms were satisfactory for this type of analysis.

Summary

The TsÊ loops of spatial vectorcardiograms were studied in 23 patients with ostium secundum, and in 7 patients with ostium primum, types of atrial septal defect. In ostium secundum defect, the TsÊ loop was sometimes oriented normally, sometimes deviated posteriorly. The biggest displacement above the isopotential point was found in the patients with severe right ventricular hypertrophy. Also found in these instances was a big angle between the maximal mean instantaneous vectors of the QRS and TsÊ loops. The magnitude of the maximal T vector and the length to width ratio of the TsÊ loop were found to be below normal values in most of the vectorcardiograms.

In the ostium primum defect, the TsÊ loop was always directed below the isopotential point, sometimes posteriorly. It was directed to the right in the patients with left ventricular hypertrophy, in whose spatial vectorcardiograms were also found the biggest values for the angle between the maximal mean instantaneous vectors of the QRS and TsÊ loops. These values were also big in patients with right ventricular hypertrophy. The diagnostic difference is presented. The magnitude of the maximal mean instantaneous T vectors was found to be slightly below normal. In these patients the lowest length to width ratio was observed.

The sJ vector in both groups of patients revealed voltage above normal. This vector was directed above the isopotential point in patients with coexistent right ventricular hypertrophy, and below the isopotential point in patients with left ventricular hypertrophy.

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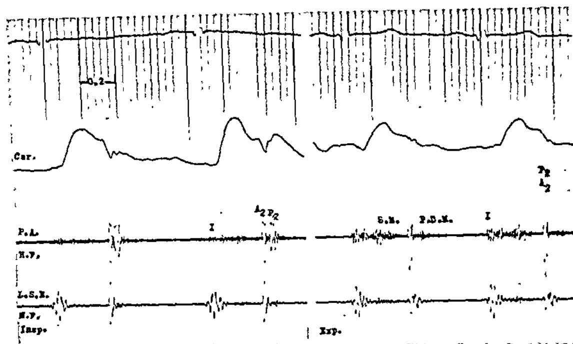


Fig. 1. Idiopathic dilation of the pulmonary artery (normal findings at catheterization) The splitting of the second sound is 0 06 sec. on inspiration, whereas on expiration, both elements of the second sound are superimposed. *Car.*: Carotid tracing *P.A.*: Pulmonary area. *H F.*: High frequency *L.S E*: Left sternal edge. *M.F*: Median frequency *I*: First heart sound A_2: Aortic element of the second sound P_2: Pulmonary element of the second sound *S.M.*: Systolic murmur *P D.M.*: Pulmonary diastolic murmur. *Insp*: Inspiration. *Exp.*: Expiration.

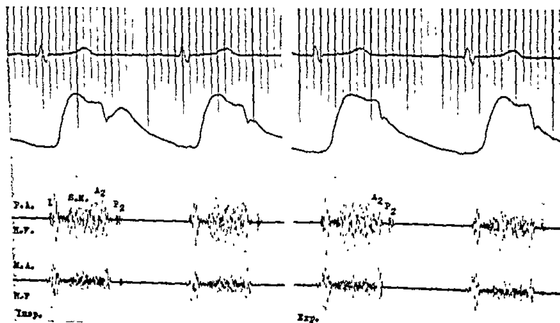


Fig. 2. Pulmonary valvular stenosis (Table I, Case 1). The splitting of the second sound is wide (0 07 sec.) and remains fixed during both phases of respiration.

The second heart sound

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The diagnostic value of analyzing the second heart sound in cardiovascular, and especially in congenital heart diseases has been recognized for a long time. In aortic stenosis, when the second sound is absent or considerably reduced, one can safely conclude that the degree of stenosis is considerably advanced.[6] In uncomplicated moderate or severe pulmonary stenosis, the pulmonary element of the second sound becomes soft. Good correlation has been found between the severity of the stenosis and the loudness of the pulmonary sound.[1,10] In severe stenosis, the pulmonary element of the second sound can be detected neither by auscultation nor by phonocardiography, and the second sound appears to be single.[10] Thus, the loudness of the pulmonary element is not only a good clinical sign for the diagnosis but also very helpful in the evaluation of the severity of the stenosis. In pulmonary hypertension, a loud and palpable pulmonary sound is an important and constant sign.[7]

Reversed split of the second sound, with prolonged closure of the aortic valve, is a valuable sign of complete left bundle-branch block, severe aortic stenosis, and patent ductus arteriosus.[15] In these two latter conditions the paradoxical characteristic of the second sound is difficult to hear and may only be detectable in a phonocardiogram.[11]

If the second sound is split, the aortic and pulmonary valves must be functioning, so that the sign serves to exclude pulmonary atresia and persistent truncus arteriosus.[15]

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In order to obtain more information about the behavior of the second heart sound in the most common conditions which affect mainly the hemodynamics of the right side of the heart, a number of patients with congenital or acquired heart diseases have been investigated by clinical examination, catheterization, and phonocardiography. Good tracings were obtained for the phonocardiographic analysis—indeed, only those patients with satisfactory tracings were admitted to the investigation, the final number being 80 out of 200 examined. Sixty-eight patients proved to be suitable for surgical treatment, and in these the clinical and catheter diagnosis was confirmed at operation. They were divided into four groups, according to the cause of the abnormal hemodynamics in the right side of the heart. In the first group, which comprised patients with pulmonary valvular or infundibular stenosis, the high pressure in the right ventricle was due to obstruction in the outflow tract of the right ventricle. In the second and third groups, which comprised, respectively, patients with ventricular septal defect and those with atrial septal defect, the abnormal hemodynamics in the right side of the heart were due either to the left-to-right shunt alone or the the combined effects of the shunt and the high pulmonary vascular resistance. In the fourth group, which comprised patients with mitral stenosis, the high right ventricular pressure was due only to the high pulmonary vascular resistance.

In all the patients with moderate or severe pulmonary stenosis (Table I and

Table III. Second heart sound during respiration in 20 patients with atrial septal defect

Case	Sex	Age (yr.)	Pulmonary arterial pressure, S/D (mm. Hg)	Right ventricular pressure, S/D (mm. Hg)	Left-to-right shunt (L.)	Pulmonary vascular resistance (units)	Splitting of the second heart sound in phonocardiograms	
							Insp. (sec.)	Exp (sec)
1.	F	35	75/46	75/5	3:1	3 8	0 03	0 03
2.	M	14	19/8	19/1	2 4:1	1	0 04	0 03
3.	F	18	38/11	25/5	2.75:1	<1	0 05	0 05
4.	F	20	18/8	24/4	3:1	<1	0 07	0 07
5.	F	38	44/16	44/0	3 3:1	3	0 03	0 03
6.	M	15	40/5	48/0	1 8.1	1	0 06	0 06
7.	F	34	90/45	95/0	1 2:1	22	0 03	0 03
8.	F	10	82/32	82/0	1 3:1	9	0 04	0 04
9.	M	32	20/2	35/0	3 3:1	1	0 06	0 06
10.	M	7	35/7	35/-3	1 9:1	1	0 05	0 05
11.	M	22	20/3	27/0	3:1	1	0 06	0 06
12.	F	44	14/12	24/0	4:1	1	0 06	0 06
13.	M	47	40/6	55/3	2:1	1 5	0 04	0 04
14.	M	27	18/6	20/0	2 5:1	1	0 08	0 08
15.	M	28	40/8	60/0	3 5.1	1	0 07	0 07
16	F	25	20/5	20/-2	1 8:1	1	0 05	0 04
17.	F	19	15/2	27/0	4 5.1	1	0 07	0 05
18.	F	10	13/5	25/0	2 5:1	1	0 07	0 06
19.	F	12	25/8	25/0	2 8·1	1	0 04	0 04
20	F	19	25/5	28/0	3 8 1	1	0 06	0 06

Table IV. Second heart sound during respiration in 20 patients with mitral stenosis

Case	Sex	Age (yr)	Pulmonary arterial pressure, S/D (mm. Hg)	Right ventricular pressure, S/D (mm. Hg)	Pulmonary vascular resistance (units)	Splitting of the second heart sound in phonocardiograms	
						Insp. (sec.)	Exp. (sec)
1.	F	33	40/3	40/0	5	0 03	0 03
2.	M	46	45/10	40/0	3	0 04	0 04
3.	F	42	30/8	35/-2	1 5	0 04	0 01
4.	F	44	80/35	80/0	14	Single	Single
5.	F	15	35/20	35/-2		0 04	0 04
6.	F	38	60/38	60/-4	5	0 02	0 02
7.	M	30	98/40	95/0		0 03	0 03
8	M	33	40/20	40/0	2	0 03	0 03
9	M	31	44/10	44/0	1 7	0 04	0 04
10.	F	45	68/13	68/0	18	0 02	0 02
11.	F	40	32/18	31/1	1 3	0 05	0 04
12.	M	38	110/50	110/4	18	0 03	0 03
13.	M	42	76/30	76/0	14	0 03	0 03
14	F	39	23/12	23/0	1	0 04	0 02
15	F	38	70/30	70/3	10	Single	Single
16	F	23	100/45	100/0	13	0 03	0 02
17.	F	24	130/75	130/6	17	Single	Single
18.	M	38	85/20	85/0	9	0 04	0 03
19.	F	45	60/35	60/0	7	0.03	0.03
20.	F	42	50/10	50/0	5	0.02	0.02

Table I. Second heart sound during respiration in 20 patients with pulmonary stenosis

Case	Sex	Age (yr.)	Pulmonary arterial pressure, S/D (mm. Hg)	Right ventricular pressure, S/D (mm. Hg)	Splitting of the second heart sound in phonocardiograms	
					Insp. (sec.)	Exp. (sec.)
1	M	9	12/5	68/0	0 07	0 07
2	F	4	18/5	125/0	0 11	0 11
3.	M	11	17/7	125/8	0 08	0 08
4.	M	31	17/9	95/4	0 10	0 10
5	M	41	12/3	60/-4	0 06	0 06
6	F	15	12/5	120/0	0 11	0 11
7.	M	47	10/0	140/0	0 14	0 14
8.	M	40	20/5	50/0	0 07	0 07
9.	F	16	12/7	100/0	0 07	0 07
10.	F	14	10/3	30/0	0 05	0 02
11	F	16	10/2	55/0	0 08	0 08
12	F	26	17/3	150/0	0 09	0 09
13	F	22	12/2	40/-5	0 08	0 05
14	F	31	8/2	142/-2	0 10	0 10
15	F	16	16/6	90/-2	0 90	0 90
16	M	10	40/7	95/-2	0 10	0 10
17	F	6	15/5	65/0	0 07	0 07
18	M	10	13/8	78/-2	0 08	0 08
19	M	25	18/7	66/-3	0 06	0 06
20	F	18	14/6	95/0	0 08	0 08

Table II Second heart sound during respiration in 20 patients with ventricular septal defect

Case	Sex	Age (yr.)	Pulmonary arterial pressure, S/D (mm. Hg)	Right ventricular pressure, S/D (mm. Hg)	Left-to-right shunt (L.)	Pulmonary vascular resistance (units)	Splitting of the second heart sound in phonocardiograms	
							Insp. (sec.)	Exp. (sec.)
1	F	22	15/5	15/0	2:1	<1	0 08	0 08
2	F	16	40/0	40/0	2:1	2 5	0 07	0 07
3.	M	28	100/45	100/3	2 5:1	6	0 03	0 03
4.	F	5	30/15	35/0	1 4:1	1	0 04	0
5.	F	5	65/29	75/0	3:1		0 03	0 03
6	F	14	15/5	15/-2	3 4:1	5	0 05	0 05
7.	F	16	55/0	62/-2	1 9:1	2 5	0 06	0 06
8.	F	11	28/14	30/5	1 4:1		0 04	0 04
9.	M	9	70/40	70/0	2:1	5	0 02	0 02
10.	F	6	26/8	33/0	1.4:1	1	0 06	0 04
11.	F	4	34/14	45/0	1.7:1		0 04	0 02
12.	M	5	65/45	65/0	4:1		0 06	0 06
13.	M	6	20/7	27/0	1 3:1	1	0 05	0 03
14.	F	11	62/12	70/-3	2 7:1	4	0 04	0 04
15.	M	17	65/40	65/0	3 6:1	6	0 03	0 03
16.	M	10	36/15	52/0	2 5:1	2 8	0 07	0.07
17.	F	8	80/30	80/0	2 4:1	3 4	0.06	0 06
18.	F	11	35/15	45/0	2:1	1	0 05	0 05
19.	M	10	120/55	120/0	1 2:1	14	0 02	0.02
20.*	M	13	30/5	62/0	1 8:1	1	0 07	0 07

*No pulmonary stenosis was found at operation.

of the heart. The right ventricle, therefore, because it has to pump more blood into the pulmonary circulation, prolongs its systole, and, hence, the pulmonary valve closes later. Because of the delay of a few seconds in the passage of blood through the pulmonary vessels, this augmented volume of blood does not reach the left side of the heart until the subsequent expiration. Thus, left ventricular filling increases, stroke volume increases, and the aortic valve closes later during expiration. Just the opposite events occur during inspiration.[5]

In patients who have high pressure in the right ventricle and right atrium, from any cause, the amount of blood which returns to the right side of the heart is probably not much influenced by respiration. Thus, the right and, of course, the left ventricular output remain fixed during both respiratory phases. Even if the atrial or ventricular septal defect in patients with abnormal pulmonary vascular resistance is repaired, the fixed split of the second sound remains unchanged so long as the high resistance influences the pressure in the right side of the heart.

Recently, in cases of atrial septal defect, the fixed split of the second sound has been attributed to the fact that the same volume of blood reaches both the right and left ventricles in each respiratory phase.[4] It is suggested that the greater quantity of blood which enters the right atrium on inspiration decreases or entirely eliminates the left-to-right shunt, so that both ventricles receive an increased flow. On expiration, also, both ventricles receive an equal amount of blood (although less than in inspiration) because the decreased portion of blood reaching the right atrium follows an increased left-to-right shunt. Thus, both elements of the second sound move together, approaching the first sound during expiration and going away from it during inspiration.[5,13]

We failed to find such a movement of the second sound in patients with atrial septal defect whose heart rate was constant throughout both phases of respiration. Also, this theory does not explain why 30 per cent of the patients with atrial septal defect retain the fixed split of the second sound even after a successful operation.[3]

The fixed and wide split of the second sound in patients with atrial septal defect was recognized very early in the evolution of our knowledge of congenital heart diseases.[2,9] The ejection systolic murmur produced by the increased pulmonary flow

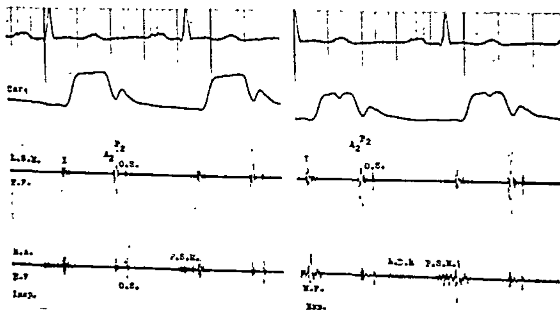


Fig. 4 Mitral stenosis (Table IV, Case 13). The second sound is closely split (0.03 sec.) and remains fixed during respiration. *P.S.M.*: Presystolic murmur. *M.D.M.*: Mitral diastolic murmur. *O.S.*: Opening snap.

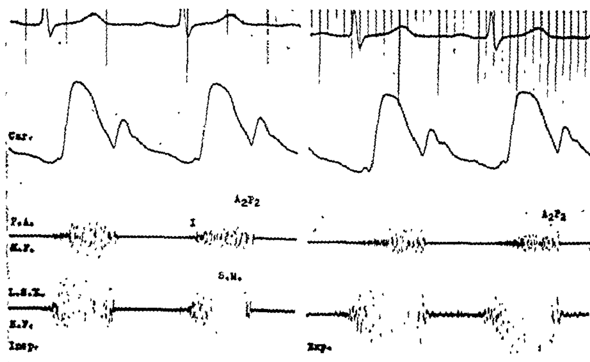


Fig. 3. Ventricular septal defect (Table II, Case 18). Both elements of the second sound remain fixed (0.05 sec.) during respiration. The aortic element is drowned by the systolic murmur.

·ig. 2) the split of the second sound was wide, and fixed during respiration. In 2, in whom the pressure gradient across the pulmonary valve was small, the second sound moved during respiration.

In most of the patients with ventricular septal defect (Table II and Fig. 3) the second sound remained fixed during respiration. In 4, the second sound moved normally; but in one (Case 10) it remained a little wider than normal during expiration (0.04 second). In these 4 the shunt was small; and in the 3 of them whose pulmonary resistance could be determined the resistance was found to be normal.

The splitting of the second sound in patients with atrial septal defect (Table III) was found to be fixed during respiration, and wide only when the pulmonary vascular resistance was normal.

The fourth group comprised patients without any shunt, and the right ventricular overload, when present, was due to mitral stenosis (Table IV and Fig. 4). In most of them the second sound was closely split, and in 4 of them it was single. Most of these patients had a very high pulmonary vascular resistance. The 2 patients (Cases 3 and 14) who had a normal pulmonary vascular resistance had a second sound which moved normally.

Discussion

It is very well known that, in normal subjects, respiration affects the time of closure of the pulmonary and aortic valves. This was recognized in 1866,[12] and was later confirmed by phonocardiography.

During inspiration, the pulmonary valve closes later and the aortic valve earlier; and during this phase, both elements of the second sound can be easily separated either on auscultation or in phonocardiograms. During expiration, on the other hand, the pulmonary valve closes earlier and the aortic valve later, so that both elements of the second sound approach each other or fuse together (Fig. 1).[4] These changes in the second sound are explained by the hemodynamic changes which occur in the two sides of the heart.[11] After inspiration the negative pressure in the mediastinum increases, and this augments the amount of blood returning to the right side

Noninfarctional $QS_{II, III, AVF}$ complexes as seen in the Wolff-Parkinson-White syndrome and left bundle branch block

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Kariv[1] has recently reported on 6 patients with Wolff-Parkinson-White syndromes whose electrocardiograms showed QS or QR complexes in Leads II, III, and AV_F. Superficially, these QS or QR configurations simulate those of acute or residual posterior or inferior wall myocardial infarctions, with resultant misinterpretation of the electrocardiogram. Failure to appreciate the presence of the Wolff-Parkinson-White syndrome or left bundle branch block, due to unusual anatomic cardiac position, compounds the difficulty of interpretation.

Accordingly, an electrocardiographic survey of patients with Wolff-Parkinson-White syndrome* or left bundle branch block who presented QS complexes in Leads II, III, and AV_F or in Leads III and AV_F was undertaken.

Materials and methods

The cases of 11 patients who had tracings which showed QS waves in Leads II, III, and AV_F, and of 23 patients who had QS complexes in Leads III and AV_F, displaying either Wolff-Parkinson-White syndrome or complete left bundle branch block, were collected at the Electrocardiographic Heart Stations, University Hospitals and the Veterans Administration Hospital, Madison, Wisconsin.

The origin of the QS complexes in Leads II, III, and AV_F, as well as the features of differentiation from residual posterior wall infarction are discussed. Correlations of the clinical history, physical findings, and chest x-ray films were made on all patients. Autopsy data were available on 6 patients.

Results

The notched QS complexes identified in Leads II, III, and AV_F of the 3 patients with the Wolff-Parkinson-White syndrome are the result of the right ventricular QS potential being reflected to the left hip (Leads II, III, and AV_F), and the rR′ of the left ventricular potential directed to the left shoulder (Leads I and AV_L) and the left precordial leads V_5 and V_6. AV_F is thus the upside down mirror image of AV_L. The initial slur of the Q wave in Leads II, III, and AV_F is, in fact, an inverted delta wave, and the total inscription time of the Q waves in these leads is equal to the total inscription time of the rR′ complex identi-

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*The electrocardiographic identification of the Wolff-Parkinson-White syndrome for the purpose of this study required the presence of a P-R interval of 0.10 second, or less, a QRS duration of 0.12 second, or more, and a well-defined delta wave at the base of the left ventricular R wave.

stops long before the second sound[11]; hence, the aortic and pulmonary elements can be seen in phonocardiograms and heard on auscultation quite easily.[11] Moreover, the pulmonary element of the second sound in half of the patients is loud and easily identified.[1-3] On the other hand, in patients with ventricular septal defect or pulmonary stenosis, it is very difficult to evaluate the second sound, because the aortic element is drowned by the systolic murmur; and in pulmonary stenosis, the softness of the pulmonary element increases the auscultatory difficulties.[10]

In all our cases of atrial or ventricular septal defect, good correlation was found between the magnitude of the shunt and the wideness of the second sound, provided that the pulmonary vascular resistance was normal and there was no obstruction in the outflow tract of the right ventricle. A big shunt with normal pulmonary vascular resistance always produces a wide split of the second sound.

In all patients with high pulmonary vascular resistance and no shunt the second sound was closely split and did not move on inspiration.

Summary

The second heart sound was studied in 80 patients with systolic or diastolic overload of the right ventricle. In patients who had moderate or severe pulmonary stenosis the second sound was wide and fixed during respiration; it was also wide and fixed in patients who had a considerable left-to-right shunt at the atrial or ventricular level. In patients who had high pulmonary vascular resistance, with or without a shunt, the second sound was closed and remained fixed during respiration. The probable mechanism of this phenomenon is briefly discussed.

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available on 4 of the 18 patients in this category. Anatomic left ventricular hypertrophy was documented in 3 of the patients, and in one case it was associated with a necrotizing arteritis. Save for several arteriosclerotic plaques in the ascending aorta, the heart was normal in the fourth patient, who died of an acute pulmonary embolus. None showed evidence of myocardial infarction, either acute or residual. Two representative electrocardiograms are shown in Fig. 3. Again, the available left precordial leads of Patient *H. B., 66* years old, only hint at the presence of a complete left bundle branch block, which is readily identified in Leads I and AV_L. Five of the patients in this category had advanced hypertensive heart disease, 6 had arteriosclerotic heart disease (4 with and 2 without associated congestive failure), and 7 showed no clinical evidence of heart disease, although 4 of these latter patients were extremely obese, which caused a horizontal placement of the heart.

Fig. 4 shows QS or QR complexes in Leads *III* and AV_F associated *with the* Wolff-Parkinson-White syndrome. Without appreciating the presence of the basic electrocardiographic configuration, one would *again consider residual posterior wall infarction* from the electrocardiographic standpoint alone. None of these patients reported pertinent cardiovascular histories.

Finally, Fig. 5 reveals QS or Qr com-

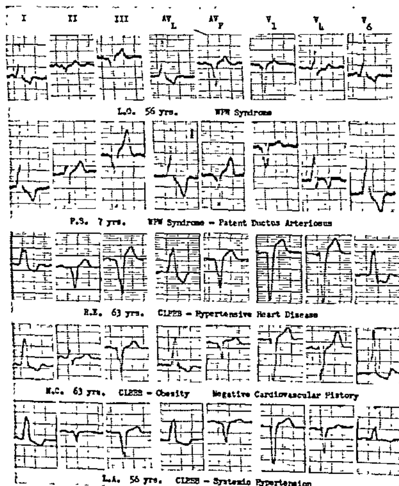


Fig. 2. $QS_{III, aVF}$ complexes associated with the WPW syndrome and complete LBBB. The grossly slurred delta wave is well seen in Lead III of Patient P. S., 7 years old. Note the grossly slurred Q waves in Leads III and AV_F of the 3 patients with complete LBBB, having an inscription time of 0.08 second.

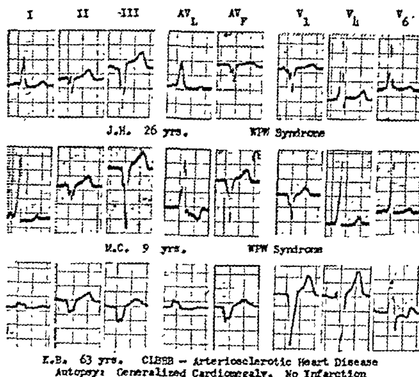


Fig. 1. $QS_{II, III, aVF}$ complexes associated with the WPW syndrome and complete LBBB. Note the similarity of the QRS configuration of Leads AV_F and V_1.

fied in Leads I, AV_L, and V_6 (0.07 to 0.09 second), dependent on the total QRS complex duration.

All 3 patients who had the Wolff-Parkinson-White syndrome had had episodes of recurrent paroxysmal tachycardia. In Fig. 1, the electrocardiograms of Patients J. H. and M. C are representative.

Eight instances of complete left bundle branch block patterns presenting QS complexes in Leads II, III, and AV_F were collected. In Fig. 1, the electrocardiogram of Patient K. B., 63 years old, is of particular note, in that the left bundle branch block is not readily identifiable in the available precordial leads, due to horizontal cardiac position, and no evidence of an acute or residual infarctional process was found at autopsy. All 8 patients in this group had organic heart disease, with roentgenographic evidence of generalized cardiomegaly. Four of these patients had arteriosclerotic heart disease, 3 had hypertensive heart disease, and 1 had rheumatic heart disease with aortic stenosis and insufficiency. Autopsy revealed aortic stenosis and left ventricular hypertrophy in the latter patient.

The electrocardiograms of 2 of the 5 patients with the Wolff-Parkinson-White syndrome and QS complexes in only Leads III and AV_F are shown in Fig. 2. Two of these patients, ages 44 and 56 years, reported bouts of paroxysmal tachycardia. A 7-year-old boy had a patent ductus arteriosus, and the other 2 patients, an 18-year-old girl with Huntington's chorea, and a 40-year-old schizophrenic, were free of cardiac disease. Only the 7-year-old boy had roentgenographic evidence of left ventricular enlargement.

Eighteen tracings with QS waves in Leads III and AV_F associated with a complete left bundle branch block were collected. Three representative tracings are shown in Fig. 2. The grossly slurred Q waves in Leads III and AV_F again result from the right ventricular potential being projected to the left hip, with AV_F the reciprocal potential of AV_L. Autopsies were

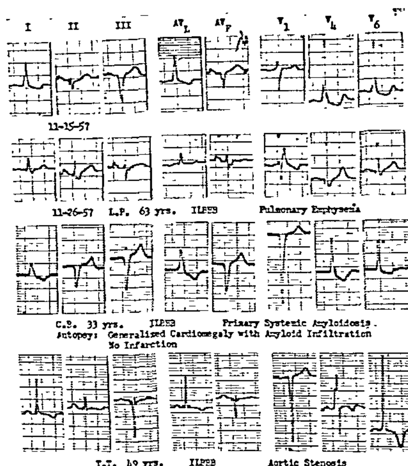


Fig. 5. QS$_{II, III, aVF}$ complexes are identified with an incomplete LBBB in Patient L. P., 63 years old, simulating those of a posterior wall myocardial infarction. He exhibited alternating incomplete LBBB and complete RBBB on repeated occasions, with the right bundle branch block present on the tracing of Nov. 26, 1957. The loss of the normal septal q wave associated with a gross slurring at the base of left ventricular R waves of Leads V$_4$ and V$_6$ (noted on the tracing of Nov. 15, 1957) suggests the presence of an incomplete left bundle branch block. The initial slurring of the QS complexes seen in Leads II, III, and AV$_F$ of Patient C. B., 33 years old, is again due to the right-to-left septal depolarization of the incomplete LBBB. The inscription time of these Q waves measures 0.06 second. Autopsy confirmed only generalized cardiomegaly with extensive amyloid infiltration of the myocardium. The Qr complexes seen in Leads III and AV$_F$ of Patient T. T., 49 years old, would cause difficulty in interpretation if the rR′ complexes identified in Leads I and AV$_L$ were not appreciated as an expression of incomplete LBBB. Superficially, the left ventricular QRS complexes identified in Leads I, AV$_L$, and V$_6$ suggest left ventricular hypertrophy.

tiple tracings. Autopsy confirmed the absence of myocardial infarction in Patient C. B., 33 years old, who died of systemic amyloidosis. The left ventricular rR′ complex of the incomplete left bundle branch block is well seen in Leads I and AV$_L$ of Patient T. T., 49 years old, who had severe aortic stenosis and anatomic left ventricular hypertrophy.

None of the 34 patients currently reported on had subjective symptomatology which suggested an acute myocardial infarction. This by no means excluded the presence of coronary artery disease. Autop-

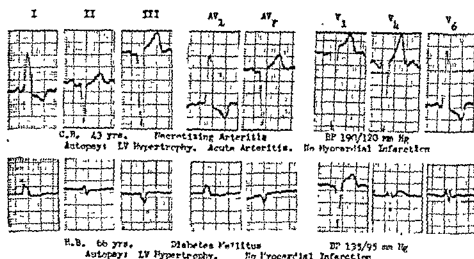


Fig. 3. QS_{III, AV_F} complexes associated with complete LBBB. Left ventricular hypertrophy without myocardial infarction was documented at autopsy. The LBBB of Patient H. B. is identified in Leads I and AV_L.

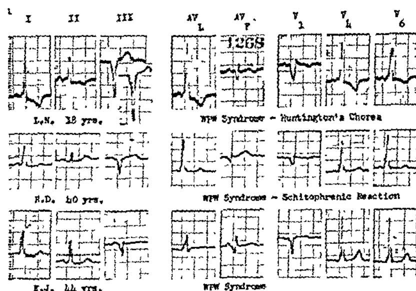


Fig. 4. QS or QR complexes seen in Leads III and AV_F associated with the WPW syndrome. Again, this configuration superficially *simulates* that of residual posterior wall myocardial infarction. The delta wave of the WPW syndrome is seen to advantage in the insert of Lead III of Patient L. N., age 18 years. The QS or QR complexes identified in Leads III or AV_F result from the right ventricular potential being subtended to the left hip.

plexes in Leads III and AV_F with instances of incomplete left bundle branch block, which also simulate posterior wall myocardial infarction. The QRS configuration of the incomplete left bundle branch block differs in no way from that of complete left bundle branch block, save for a QRS duration of 0.08 to 0.10 second. Patient L. P. of Fig. 5 had bouts of paroxysmal tachycardia and suffered from pulmonary emphysema and the effects of the hyperventilation syndrome. He showed alternating incomplete left bundle branch block and complete right bundle branch block on mul-

and complete left bundle branch block, with common anatomic features of left ventricular hypertrophy and septal and left ventricular fibrosis. Scott and Norris[17] made similar observations in a more detailed electrocardiographic and pathologic correlation study of left bundle branch block, as did Johnson and co-workers[18] in an analysis of 555 patients with electrocardiographic evidence of complete left bundle branch block. Hypertension (342 instances) and arteriosclerosis, viz., coronary artery disease (122 instances), were the predominant clinical features in this latter series. There was no apparent etiology in 71 patients. The most common cause of death was congestive heart failure or myocardial infarction.

Summary

We have presented 34 instances of tracings which showed QS complexes in Leads II, III, and AV_F or Leads III and AV_F, from patients with Wolff-Parkinson-White syndrome and complete left bundle branch block. Superficially, this electrocardiographic configuration may simulate that of acute or residual posterior wall myocardial infarction.

This QS configuration results from the right ventricular potential (QS complex) being reflected in Leads II, III, and AV_F, with the left ventricular potential (slurred R or rR′ complex) being projected to the left shoulder (Leads I and AV_L).

The QS configuration is characterized by an initial downward notching, due to the delta wave in instances of the Wolff-Parkinson-White syndrome, and to the initial right-to-left septal depolarization in instances of left bundle branch block. The inscription time of this Q wave measures 0.07 to 0.09 second, being equal to the inscription time of the slurred R or rR′ complexes in the left ventricular leads. In sharp distinction, the Q wave of a posterior wall myocardial infarction measures 0.035 to 0.04 second in duration, and the QS or Qr complex is often notched on the upstroke, with preservation of a late r wave, albeit of low amplitude.

Coronary artery disease and hypertensive heart disease are the two most common clinical entities associated with complete left bundle branch block. None of the 34 patients currently reported on, however, had a history of myocardial infarction. Autopsy, which was available on 6 patients, failed to reveal residuals of myocardial infarction.

A broader appreciation of the QS configuration in Leads II, III, and AV_F associated with the Wolff-Parkinson-White syndrome or left bundle branch block is required. Failure in this regard may result in serious misinterpretation of the electrocardiogram.

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sies were available on 6 patients. Anatomic left ventricular hypertrophy was the predominant finding, and, specifically, myocardial infarctional residuals were not observed.

Discussion

The tendency for electrocardiograms in cases of the Wolff-Parkinson-White syndrome to show QS complexes in Leads II, III, and AV_F which simulate those of posterior wall infarction has been stressed by Wolff,[2] Levine and Beeson,[3] Kariv,[1] and Hejtmancik and Herrmann.[4] Although Wolff and White[5] originally believed that the QS configuration was commonly seen, this was not confirmed by subsequent work.[2,6-8] Levine and Beeson[3] published two examples of the $QS_{II, III}$ complexes in a 13-year-old boy and a 36-year-old adult. Of the 6 patients reported on by Kariv,[1] 3 had unequivocal $QS_{II, III, AVF}$ complexes, which, in one patient, disappeared when a normal sinus rhythm was established; this is similar to what was seen in the case of Patient L. P. (Fig. 5) of the current study. The other 3 patients exhibited either QR or qR complexes in Leads III and AV_F.

The notching on the downstroke of the $QS_{II, III, AVF}$ complexes of the Wolff-Parkinson-White syndrome and complete left bundle branch block is the result of the inverted delta wave of the Wolff-Parkinson-White syndrome and the septal r wave of the left bundle branch block. Lepeschkin[9] has previously demonstrated that if the delta wave (the initial slur of the R deflection) has a left axis deviation of more than −30 degrees, it will appear as a Q wave in Leads II, III, and AV_F. Zang, Herrmann and Hejtmancik[10] were similarly impressed by the leftward tendency of QRS activation with instances of "nondelayed conduction" (Wolff-Parkinson-White).

Utilizing vectorcardiographic analysis, Bleifer and associates[11] observed that the QS wave in Leads II, III, and AV_F was apt to occur if the delta wave of the QRSsÊ loop was initially directed superiorly.

Our current data have reaffirmed the fact that the inscription time of the Q wave of the QS configuration seen in Leads II, III, or AV_F is equal to the inscription time of the left ventricular slurred R or the rR' complex of the Wolff-Parkinson-White syndrome or left bundle branch block, measuring 0.07 to 0.09 second (from the beginning of the isoelectric line to the nadir of the Q wave). This measurement is in sharp distinction to that of a posterior wall infarction, in which condition the measurement characteristically is 0.035 to 0.04 second. The notching of the QS complexes of Leads II, III, and AV_F associated with the Wolff-Parkinson-White syndrome or complete left bundle branch block is identified on the proximal downstroke of the Q wave. This is not the feature of a posterior wall infarction, in which case the notching is usually noted on the ascending limb of the subsequent rudimentary r wave.

From the standpoint of electrocardiographic interpretation, there is general agreement that the QS complex inscribed in Leads II, III, and AV_F in instances of Wolff-Parkinson-White syndrome or left bundle branch block is the result of the right ventricular potential being reflected to the left hip. Wilson[12] previously stated that in the presence of a left bundle branch block, the potential in the left arm is usually of left ventricular origin, and the potential in the left leg is of right ventricular origin. The figures in this paper indicate the frequent presence of QS complexes in Lead V_1.

Somerville and Wood,[13] Sodeman and coworkers[14] and Dressler and associates[15] found, respectively, that $QS_{III, AVF}$ complexes occurred in 30, 33, and 25 per cent of the cases of uncomplicated left bundle branch block (noninfarctional). Dressler and associates[15] specifically commented that a QS_{II} was never present in cases of uncomplicated left bundle branch block. This statement is not justified from our current data nor from other isolated autopsied material. Only recently, Rhoads, Edwards and Pruitt[16] stated that the $QS_{II, III, AVF}$ configurations associated with a left bundle branch block are "supportive evidence" of posterior wall infarction. The degree of horizontal placement of the heart determines, in part, whether the QS complex of the Wolff-Parkinson-White syndrome or left bundle branch block will be identified only in Leads III and AV_F or in Leads II, III, and AV_F.

Hypertensive and arteriosclerotic heart disease predominated in our patients who had QS waves in Leads II, III, and AV_F

Aortic stenosis in adults. Evaluation of diagnostic criteria in the selection of patients for surgical treatment

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Reconstructive procedures in the treatment of aortic stenosis have recently shown such promise that it may be possible to offer patients surgical treatment at an earlier stage of their disease than has been considered justifiable with the earlier commissurotomy techniques.[1] Since, in addition, the hazards of surgical treatment are increased when the disease is advanced,[2] the early recognition of suitable patients is important. It is generally agreed that this cannot be done adequately by clinical examination alone.[3] An objective measurement of the severity of the obstruction is provided by the systolic gradient across the aortic valve, which may be obtained from simultaneous recordings of the pressure in the left ventricle and that in the brachial artery.[4] In relating the magnitude of the gradient to the severity of the obstruction, allowance must be made for increased stroke flow due to significant coexistent aortic regurgitation, and reduced stroke flow secondary to heart failure.[5]

The purpose of the present study is to evaluate routine diagnostic aids, including the electrocardiogram, x-ray films, and the direct recording of brachial arterial pressure, in the assessment of aortic stenosis. The findings provided by these means are correlated with the peak systolic gradient, which is used as an index of severity.

Material and methods (See Table I)

The electrocardiographic, radiologic, and brachial arterial pressure data of 21 patients who underwent left ventricular puncture between 1958 and 1961 were studied. Selection for left ventricular puncture had been based on the diagnosis or suspicion of a predominantly obstructive lesion amenable to surgical treatment.

The ages of the patients ranged from 24 to 58 years; the mean age was 44.4 years.

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Thirteen (62 per cent) were females (mean age of 47.8 years), and 8 (38 per cent) were males (mean age of 38.9 years). All patients were white. A history of rheumatic fever was obtained in 8 (38 per cent). Eleven (52 per cent) had had angina, and one had had effort syncope. Four (19 per cent) had been in congestive failure at the time of admission to the hospital. All had a loud ejection murmur which was transmitted to the neck. Fourteen (67 per cent) had a systolic thrill, and 13 (62 per cent) had a high-pitched, early diastolic murmur.

Percutaneous left ventricular puncture with a No. 18 or No. 20 gauge thin-walled needle was carried out according to Brock's method.[4] A No. 18 or No. 20 gauge needle was placed in the brachial artery, and pressures in both sites were recorded using strain-gauge manometers* and a direct-writing two-channel recorder† with a paper speed of 25 mm. per second. Pressures in the left ventricle and brachial artery were recorded simultaneously in 16 patients (76 per cent), and in immediate succession in 5 (24 per cent). Cardiac outputs were not determined.

Electrocardiograms were analyzed according to Grant's criteria.[5] Fluoroscopy and interpretation of the x-ray films had been carried out by the hospital radiologic staff.

The patients were arbitrarily divided into two groups: those with a peak systolic gradient above 45 mm. Hg constituted Group A, and those with a gradient below 45 mm. Hg, Group B. This division was made to simplify presentation of the results, and to have one group which could serve as a basis for comparison with the other. The dividing line between groups was chosen, because, with relatively pure stenosis, a gradient across the aortic valve above 50 mm. Hg has been suggested as a criterion of severity sufficient to warrant surgical treatment.[1] In the range of gradients in the present series there happened to be a gap between 20 and 45 mm. Hg, so that the groups fell naturally into the separate ranges of 45 to 135 and 0 to 20 mm. Hg.

No serious complications were observed to be due to left ventricular puncture.

*Statham Instruments, Inc., Los Angeles, Calif.
†Sanborn Company, Waltham, Mass.

Results (See Table II)

Group A (systolic gradient above 45 mm. Hg). This group consists of 13 patients (62 per cent of the total), with a range of ages from 27 to 58 (mean 46.8 years); 8 (62 per cent) were females, and 5 (38 per cent) were males.

The peak systolic gradient ranged from 45 to 135 mm. Hg (mean 98 mm. Hg), the left ventricular systolic pressure from 145 to 265 mm. Hg (mean 205 mm. Hg), the brachial arterial systolic pressure from 95 to 130 mm. Hg (mean 108 mm. Hg), and the arterial pulse pressure from 35 to 65 mm. Hg (mean 51 mm. Hg). The left ventricular end-diastolic pressure was elevated to between 15 and 25 mm. Hg in 5 patients (38 per cent). In one there was pulsus alternans.

In the brachial arterial pressure recordings the duration of the systolic upstroke ranged from 0.17 to 0.26 second (mean 0.20 second). In 7 patients (54 per cent) it was above 0.20 second, which is the extreme upper limit of normal according to Hancock and Abelmann[7]; in 5 (38 per cent) it was above 0.21 second.

In one patient (L.W.) in this group the diagnosis of idiopathic hypertrophic subaortic stenosis was established by analysis of simultaneous tracings of left ventricular and brachial arterial pressure. After premature ventricular contractions the arterial pulse pressure decreased in association with an increased left ventricular systolic pressure.[8] Another patient (M.E.) in this group was found later at operation to have the same condition; no premature contractions occurred while pressures were being recorded.

Analysis of the electrocardiograms suggested that left ventricular hypertrophy was present in all 13 patients (100 per cent), and left ventricular strain in 9 (69 per cent). Left ventricular ischemia was present in 4 (31 per cent), and left axis deviation which exceeded −30 degrees, in 2 (15 per cent). All 8 patients with a gradient of 100 mm. Hg or greater had electrocardiographic left ventricular strain, whereas only one of the 5 with a gradient between 45 and 90 mm. Hg had this abnormality.

Radiologic evidence of left ventricular enlargement was reported in all but one

Table I

Number	Patient	Age, Sex	Pressures* (mm Hg)			SUD (sec.)	ECG†				X-ray‡			Operated on	Died
			LV	BA	PSG		LVH	LVS	LVI	LAD	LVE	Ca.Ao	PSD		
1.	D.A.	34, M	172/5	120/55	52	0 24	+	−	+	−	+	+	+	+	
2.	O.A.	58, M	165/25	95/55	70	0 20	+	+	−	−	+	−	−	+	
3.	E.B.	58, F	230/10	95/60	135	0 22	+	+	−	−	+	+	+	+	+
4.	P.B.	46, F	150/2	147/75	3	0 11	+	−	+	−	+	−	+		
5.	R B.	45, F	185/15	170/100	15	0 21	−	−	+	−	+	−	−		
6	R.B.	24, M	120/0	106/40	14	0 13	+	−	+	−	+	−	−		
7.	M C.	41, F	185/10	165/60	20	0 18	−	−	+	−	+	−	−		
8.	G.D.	49, M	130/0	120/55	10	0 16	−	−	+	+	+	+	+		
9.	M.E.	41, F	225/25	125/60	100	0 21	+	+	−	−	+	−	−	+	
10.	C.G.	48, F	200/10	100/50	100	0 20	+	+	−	−	+	+	−	+	
11.	M H.	44, F	145/10	145/75	0	0 18	+	−	−	+	+	−	−		
12.	E.J.	46, F	100/0	85/45	15	0 21	−	−	+	−	−	−	−		
13.	R.M.	29, M	135/5	115/75	20	0 12	−	−	+	−	+	+	−		
14.	R.M.	32, M	150/5	95/50	55	0 18	+	−	+	−	+	−	−	+	
15.	E.P.	42, F	145/10	100/50	45	0 22	+	−	+	−	−	−	−	+	
16.	D R.	53, F	225/10	125/65	100	0 32	+	+	−	+	+	−	−	+	+
17.	L.R.	27, M	250/16	115/65	135	0 26	+	+	−	−	+	+	+	+	+
18.	H.T.	58, M	212/23	95/48	117	0 21	+	+	−	−	+	+	−	+	
19.	L.W.	47, F	190/15	100/50	90	0 10	+	−	+	+	+	−	−	+	+
20.	O.W.	56, F	240/10	105/45	135	0 20	+	+	−	−	+	+	+		
21.	L.W.	54, F	265/5	130/85	135	0 17	+	+	−	−	+	+	−	+	
Total Number—21							16	9	11	4	19	9	6	12	4
Per cent—100							76	43	52	19	90	43	29	57	19

*LV: Left ventricle. BA: Brachial artery. PSG: Peak systolic gradient. SUD: Systolic upstroke duration

†LVH: Left ventricular hypertrophy. LVS: Left ventricular strain. LVI: Left ventricular ischemia. LAD: Left axis deviation.

‡LVE: Left ventricular enlargement. Ca Ao: Calcification of aortic valve. PSD: Poststenotic dilatation of aorta.

N.B. In Cases 3, 4, 5, 13, and 18 the pressures were recorded in immediate succession, and in Case 4 the femoral arterial pressure was recorded.

In the brachial arterial pressure recordings the duration of the systolic upstroke ranged from 0.11 to 0.21 second (mean 0.16 second); in 2 patients (25 per cent) it was above 0.20 second, which is the upper limit of normal, but in none did it exceed 0.21 second.

Analysis of the electrocardiograms suggested that left ventricular hypertrophy was present in 3 patients (37 per cent), left ventricular ischemia in 7 (87 per cent), and left axis deviation which exceeded −30 degrees in 2 (25 per cent). No patients in this group had left ventricular strain.

Radiologic evidence of left ventricular enlargement was reported in all but one patient (87 per cent), calcification of the aortic valve in 2 (25 per cent), and poststenotic dilatation of the aorta in 2 (25 per cent).

No patient in this group underwent repair of the aortic valve.

Discussion

In the analysis of the brachial arterial pressure recording the most significant abnormality in aortic stenosis is prolongation of the duration of the systolic upstroke.[7] In the present study the duration of the systolic upstroke was greater than 0.21 second only in the group with gradients above 45 mm. Hg; this occurred in 5 (38 per cent) of Group A. This is comparable with the finding of Hancock and Fleming[9] that the duration of the upstroke was greater than 0.22 second in 17 (45 per cent) of 38 patients with significant stenosis. Thus, in a given patient the upstroke time is of no diagnostic value unless it exceeds the limits which are indicated above.

In many studies of aortic stenosis the electrocardiographic abnormality (leaving aside conduction defects and abnormalities of rhythm) has been evaluated on the basis of left ventricular hypertrophy,[3,10,11] and left ventricular hypertrophy and the depth of T-wave inversion in Leads V_5 and V_6.[9] Although such measurement and classification of the T abnormality is convenient, it may be misleading unless it takes into account the relationship of the T vector to the different orientations of the QRS vector in space. The use of the QRS-ST-T angle to indicate left ventricular strain appears to be more logical, since it relates the T to the QRS vector. The presence of left ventricular strain was found to correlate well with a high systolic gradient across the aortic valve in the present series; in 8 (89 per cent) of those who showed left ventricular strain, the gradient was 100 mm. Hg or greater, and in the other one it was 70 mm. Hg.

In view of the widely held belief that left axis deviation occurs when the left ventricle is disproportionately enlarged,[12] it is worth noting the low incidence of left axis deviation in those subjects with high gradients. As Grant[13] has pointed out, hypertrophy itself is not responsible for the left axis deviation, for even the most marked left ventricular hypertrophy is accompanied by normal QRS axis direction in the majority of cases. Our finding of left axis deviation in only 2 patients (15 per cent) in Group A, all 13 of whom had electrocardiographic evidence of left ventricular hypertrophy, is in agreement with this.

In a recent study of the radiologic findings in 69 patients with proved severe aortic stenosis, it was found that left ventricular enlargement was demonstrable in 90 per cent, calcification of the aortic valve in 85 per cent, and poststenotic dilatation of the aorta in 55 per cent.[14] Corresponding figures in Group A of our series are 92, 54, and 31 per cent. In the above-mentioned report,[14] no correlation could be found between the severity of the aortic stenosis, as estimated by the magnitude of the peak systolic gradient, and the degree of left ventricular enlargement or the degree of poststenotic dilatation. In view of the small number of patients in our study, we do not attempt to make any corresponding correlation.

The rapid deterioration in the final stage of aortic stenosis has frequently been commented on,[2] and at this stage, severe stenosis may produce a spuriously low gradient if stroke flow is reduced.[5] Since the S-T and T vector abnormality of left ventricular strain is related to elevated pressure in the left ventricle,[6] when the gradient falls in association with failure, left ventricular strain will tend to disappear and so reduce the diagnostic value of the electrocardiogram in this respect.

Table II

Parameter		Group (number of patients)		
		A (13)	B (8)	A + B (21)
Peak systolic gradient				
Above 45 mm. Hg	Number	13	0	13
	%	100	0	62
Below 45 mm. Hg	Number	0	8	8
	%	0	100	38
Systolic upstroke duration				
0.22 sec. or above	Number	5	0	5
	%	38	0	24
0.21 sec. or below	Number	8	8	16
	%	62	100	76
ECG*				
LVH	Number	13	3	16
	%	100	38	76
LVS	Number	9	0	9
	%	69	0	43
LVI	Number	4	7	11
	%	31	87	52
LAD	Number	2	2	4
	%	15	25	19
X-ray†				
LVE	Number	12	7	19
	%	92	87	90
CaAo	Number	7	2	9
	%	54	25	43
PSD	Number	4	2	6
	%	31	25	29

*LVH: Left ventricular hypertrophy. LVS: Left ventricular strain. LVI: Left ventricular ischemia. LAD: Left axis deviation.
†LVE: Left ventricular enlargement. CaAo: Calcification of aortic valve. PSD: Poststenotic dilatation.

patient (92 per cent), calcification of the aortic valve in 7 (54 per cent), and post-stenotic dilatation of the aorta in 4 (31 per cent).

Twelve patients (92 per cent) of this group were operated upon under direct vision; the other one did not consent to have the operation. If the 2 patients with idiopathic hypertrophic subaortic stenosis are excluded, examination of the aortic valve at operation confirmed that stenosis was the predominant lesion in 10. In 9 patients there was calcification of the valve, and in one, fibrous fusion only.

Of the 12 patients operated upon, 3 (25 per cent) with aortic stenosis died from bleeding into the mediastinum within 24 hours of operation, and one (L. W.) with hypertrophic subaortic stenosis died from left ventricular failure on the sixth postoperative day.

Group B (systolic gradient below 45 mm. Hg). This group consists of 8 patients (38 per cent of the total), with a range of ages from 24 to 49 (mean 40.5 years); 5 (63 per cent) were females, and 3 (37 cent) were males.

The peak systolic gradient ranged from 0 to 20 mm. Hg (mean 12 mm. Hg), the left ventricular systolic pressure from 100 to 185 mm. Hg (mean 144 mm. Hg), the brachial arterial systolic pressure from 85 to 170 mm. Hg (mean 132 mm. Hg), and the arterial pulse pressure from 40 to 105 mm. Hg (mean 66 mm. Hg). The left ventricular end-diastolic pressure was elevated (15 mm. Hg) in one patient. In none was there pulsus alternans.

Experimental and laboratory reports

The hemodynamic effects of amyl nitrite and phenylephrine in patients with mitral stenosis and severe pulmonary hypertension

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Studies of the action of amyl nitrite and phenylephrine in normal subjects[1] have shown the predominant effect of these drugs on the systemic circulation. Amyl nitrite causes a marked drop in systemic pressure, but leaves pulmonary arterial pressure relatively unchanged. On the other hand, phenylephrine markedly raises the systemic pressure and causes a slight rise in the pulmonary arterial pressure, which is due predominantly to an increase in the pulmonary arterial wedge pressure. The striking reduction in the pressure difference between the left and the right ventricles after amyl nitrite, and the increase after phenylephrine, were related to the changes in intensity of murmurs due to ventricular septal defect unassociated with pulmonary hypertension.[1-2]

In ventricular septal defect with severely elevated pulmonary arterial pressures, the flow through the large defect is mainly dependent upon the relative resistances of the pulmonary and systemic circuits. In this situation the murmurs of ventricular septal defect often failed to soften after the administration of amyl nitrite or to increase after phenylephrine, and even behaved in a paradoxical fashion. Thus, they became loud after amyl nitrite had been inhaled, and they softened after phenylephrine.[3] This paradoxical behavior of the murmur was shown to be associated with a greater fall and rise in pulmonary arterial pressure than in systemic pressure after amyl nitrite and phenylephrine, respectively. In the absence of measurements of flow it could only be inferred that responses were brought about by appropriate changes in pulmonary vascular resistance.

This study was undertaken to investigate quantitatively the effects of amyl nitrite and phenylephrine in patients with severe pulmonary hypertension. Subjects with severe pulmonary hypertension without intracardiac shunts were selected so that clear separation of pulmonary and systemic pressures could be obtained and estimation of pulmonary blood flow made by dye-dilution studies.

Material and method

Eight patients with severe mitral stenosis, which was subsequently proved by

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Summary and conclusions

Twenty-one patients with the clinical diagnosis of significant aortic stenosis had been investigated by means of percutaneous left ventricular puncture, and the peak systolic gradient obtained from simultaneous left ventricular and brachial arterial pressure recordings.

The purpose of the present study is to evaluate routine diagnostic aids in the detection of aortic stenosis which results in a significant gradient across the aortic valve. The gradient is correlated with the arterial pressure contour and with electrocardiographic and radiologic findings.

The patients are arbitrarily divided into two groups, those with a gradient above 45 mm Hg (13 or 62 per cent), and those with a gradient below 45 mm. Hg (8 or 38 per cent). The presence of dominant obstruction had been confirmed at operation under direct vision in 12 (92 per cent) of the first group.

In the brachial arterial pressure recording a systolic upstroke duration of 0.22 second or more was present only in the first group (5 patients or 38 per cent).

Electrocardiographic evidence of left ventricular hypertrophy was present in all 13 patients (100 per cent) of the first group, but in only 3 (37 per cent) of the second group, whereas left ventricular strain was found only in the first group (9 or 69 per cent); in 8 (89 per cent) of those with left ventricular strain the gradient was 100 mm. Hg or greater. Thus, left ventricular strain appears to be the finding that is most suggestive of a high gradient.

Radiologic evidence of left ventricular enlargement was reported in a high proportion of both groups, 12 (92 per cent) and 7 (87 per cent), respectively.

The conclusion from this study is that the two most useful criteria (provided by routine diagnostic aids) of aortic stenosis which results in a significant transvalvular gradient are the presence of electrocardiographic left ventricular strain, and a systolic upstroke duration in the brachial arterial pressure recording of 0.22 second or longer.

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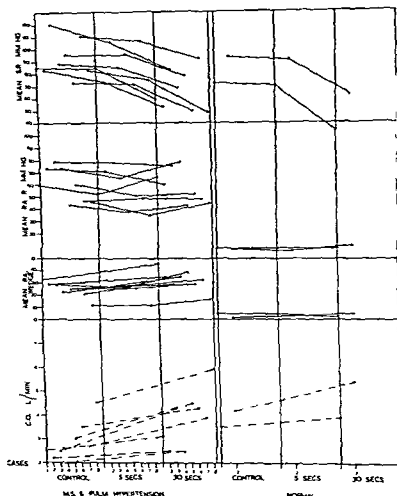


Fig. 1. Hemodynamic effects of inhalation of amyl nitrite. The three columns on the left show the mean systemic, pulmonary arterial, and wedge pressures and flow in 8 patients with mitral stenosis and pulmonary hypertension before, 5 seconds after, and 30 seconds after they had inhaled amyl nitrite. On the right, the results in 2 normal subjects previously studied[1] are shown for comparison. In the subjects with mitral stenosis, systemic pressure falls as in normal subjects. Pulmonary arterial pressure falls slightly at the 5-second period in 5 patients, but in most cases at the 30-second period is not significantly different from the control level. Wedge pressure rises slightly and cardiac output increases.

tion of the primary deflection of the dilution curve and at the time of maximal systemic hypotension. In Patients 1,2,4,5, and 8 there was a slight initial fall in pulmonary arterial pressure at the 5-second period before any real effect on systemic pressure became evident (Fig. 2). In the other 3 patients there was no real change.

At the 30-second period, Patients 3,5,7, and 8 showed no significant change from the control level. Patients 1 and 4 showed a very slight increase, and Patients 2 and 6 showed a slight fall in mean pulmonary arterial pressure. In all patients, systemic pressures dropped sharply, and in all except one (Patient 2) a tachycardia developed, as occurs in normal subjects beginning some 10 seconds after the inhalation of amyl nitrite has started.

All patients except Patient 3 showed a moderate increase in pulmonary arterial wedge pressure during the later phase of maximal effect of the drug on systemic pressure.

operation, and with mean pulmonary arterial pressures between 43 and 93 mm. Hg, were studied during routine cardiac catheterization. Atrial fibrillation was present in one (Patient 7). No patient was in frank left or right heart failure at the time of study, but all except one (Patient 8) were severely disabled by low resting cardiac outputs.

Catheterization of the right side of the heart was carried out from the right arm; one catheter was wedged in the pulmonary artery to record the pulmonary arterial wedge pressure, via a strain-gauge manometer. A second catheter was placed in the main pulmonary artery to record pulmonary arterial pressures, on a capacitance manometer. Systemic arterial pressure was recorded by a needle in the brachial or radial artery, on an inductance manometer; and another needle was placed in a second systemic artery, usually the femoral, in order to record systemic dilution curves. All pressure tracings were recorded on a six-channel N.E.P. photographic recorder, and the zero level was taken at mid-chest level, with the patient in the recumbent position.

The use of three different types of manometer is not ideal for this type of study, but in order to minimize possible errors, each transducer was carefully calibrated to give identical galvanometric deflections for a given pressure obtained from a mercury manometer. Previous experience with these instruments had shown that the calibrations remain accurate for the duration of a catheter study. The notorious tendency for base-line drift to occur with the capacitance manometer was minimized by restricting its use to record pulmonary arterial pressure on the sensitivity setting of 100 mm. Hg, where the drift is less pronounced. Zero levels were also recorded throughout the procedure before and after each tracing. Used in this way, no significant base-line drift was detected.

Cardiac output was determined from indicator-dilution curves recorded at the femoral artery after the injection of 5 mg. of indocyanine green into the pulmonary artery. The densitometer (Norman N.E.P.) was calibrated by drawing through it known concentrations of dye in the patient's blood and constructing a three-point calibration curve.

The cardiac output was estimated by dividing the dose of dye times 60 by the area under the curve. Recirculation was excluded by replotting the downstroke of the curve on a semilogarithmic basis, as in the standard Hamilton method. Pulmonary arterial, wedge, and systemic pressures and the dye-dilution curves were recorded simultaneously during the first control period.

Thereafter the patient was given a crushed vitrella containing 3 minims of amyl nitrite which was to be inhaled for 15 to 20 seconds, and as soon as the fall in systemic pressure occurred, a dilution curve was once more recorded, during the maximal systemic hypotensive phase of the drug; again, all pressures were recorded simultaneously.

A second control period was then established, after the effect of the amyl nitrite had worn off, and pressures and flow were recorded simultaneously. Thereafter, phenylephrine in a dose of 0.5 to 1.0 mg. was injected into the main pulmonary artery or into a peripheral vein, and during the late phase of systemic hypertension and bradycardia a dye curve was recorded. In one subject, phenylephrine was injected into the wedged catheter so that its effects would first be observed on the systemic circuit.

Identical studies were performed in 2 additional patients without mitral stenosis. One suffered from pulmonary hypertensive cor pulmonale due to a diffusion defect, and the other, from idiopathic pulmonary hypertension. In the latter patient the wedge pressure could not be obtained.

All studies were made with the patient in the recumbent posture under mild barbiturate sedation.

Results

The results in 8 patients who had mitral stenosis are presented.

1. The response to amyl nitrite. The data are presented in Table I and Fig. 1. Measurements were made at two points: the first at 5 seconds after the inhalation of amyl nitrite had started, and the second some 30 seconds later during the inscrip-

Pulmonary artery		Wedge		CO (L./min.)	PVR (Units)	TSR (Units)	Heart rate
S.D.	Mean	S.D.	Mean	(Dye)			
87/45	59	37/27	32	2.5	10.8	34.0	95
77/40	52	45/32	38				95
95/52	66	50/40	45	3.1	6.8	19.0	120
85/50	61	40/32	34	2.5	10.8	33.5	95
		30/27	29				105
162/52	89	48/42	44	1.6	28.1	70.6	48
105/57	75	30/26	28	2.2	21.4	37.8	108
100/55	70	38/30	31				
90/45	60	38/30	34	2.5	10.4	21.2	108
110/60	72	28/26	27	2.0	22.5	42.5	108
125/75	92	18/14	16				
135/75	95	30/26	28	1.8	37.2	56.7	108
115/60	78	30/25	28	2.5	20.0	48.0	54
110/60	77	32/23	26				
105/60	75	30/25	28	4.3	10.9	19.3	96
110/60	77	25/20	23	2.9	18.6	39.7	66
130/75	93	18/12	15				90
150/75	100	40/35	38	2.7	23.0	45.5	66
120/50	73	30/15	22	2.0	25.5	44.0	96
105/45	65	30/25	28				
125/55	78	40/30	35	2.5	17.2	27.2	114
120/45	70	25/15	20	1.8	27.8	48.9	96
180/70	103	15/10	12				96
140/50	80	20/15	18	1.3	47.7	90.0	54
80/25	43	32/18	25	3.0	6.0	31.6	60
60/25	37	38/20	26				
67/32	42	42/35	38	4.5	0.9	17.3	114
77/30	46	32/28	30	3.0	5.3	35.0	72
115/75	88	12/8	10				102
140/50	80	45/39	42	2.7	14.1	50.8	42
100/40	60	28/22	25	3.5	10.0	20.8	64
80/35	56	30/20	25				
82/37	52	32/25	29	4.3	5.4	11.6	84
95/45	62		20	3.8	11.0	23.2	66
118/57	77		5				84
120/40	67		15	3.4	15.3	33.8	54
87/25	46	27/15	21	2.7	9.4	40.7	54
85/29	48	37/20	28				
87/28	48	45/20	32	3.9	4.10	23.6	60
87/32	50	26/16	21	3.0	9.7	35.3	54
107/45	65	16/8	12				66
115/37	63	29/19	24	2.0	19.5	65.0	36
60/38	45		11	4.5	7.6	18.6	96
50/28	35		11				
58/37	44		16	5.9	4.8	8.1	120
62/38	46		14	4.4	7.3	20.0	96
81/50	60		9				102
110/55	73		13	2.7	22.2	48.1	48

A.N.—Amyl nitrite. P.E.—Phenylephrine. PVR—Pulmonary vascular resistance. TSR—Total systemic resistance.

slightly higher values; the mean increase in cardiac output was 36 per cent (range, 13-72).

As a result of the decrease in pressure difference across the lungs and an increase in pulmonary blood flow, the calculated vascular resistance, expressed in simple units obtained by dividing the mean pres-

Table I. Pressures (mm. Hg)

Patient, Sex, Age	Diagnosis	State	Systemic artery	
			S.D.	Mean
1 C.F., 33	Pure mitral stenosis with severe, pulmonary hypertension	Control	112/72	85
		A.N. 5 sec.	110/72	84
		A.N. 30 sec.	80/48	59
		Control	108/72	84
		P.E. early	96/60	72
		P.E. late	140/60	113
2. E.M., 41	Mitral stenosis with severe pulmonary hypertension	Control	110/70	83
		A.N. 5 sec.	100/60	73
		A.N. 30 sec.	90/50	53
		Control	115/70	85
		P.E. early	70/50	57
		P.E. late	125/85	102
3 B.M., 25	Mitral stenosis with severe pulmonary hypertension	Control	170/95	120
		A.N. 5 sec	125/95	105
		A.N. 30 sec.	100/75	83
		Control	165/90	115
		P.E. early	115/75	92
		P.E. late	190/90	123
4 C.F., 28	Mitral stenosis with severe pulmonary hypertension	Control	115/75	88
		A.N. 5 sec.	110/72	85
		A.N. 30 sec.	90/55	68
		Control	115/75	88
		P.E. early	115/75	88
		P.E. late	170/90	117
5 B.F., 18	Mitral stenosis, severe	Control	135/75	95
		A.N. 5 sec.	135/75	95
		A.N. 30 sec	95/55	78
		Control	145/85	105
		P.E. early	65/45	52
		P.E. late	190/110	137
6 E.M., 36	Severe pulmonary hypertension. Mitral stenosis	Control	110/60	73
		A.N. 5 sec.	102/55	71
		A.N. 30 sec.	72/40	50
		Control	125/70	88
		P.E. early	85/60	67
		P.E. late	115/95	115
7 E.F., 52	Mitral stenosis with severe pulmonary hypertension. A.F.	Control	150/90	110
		A.N. 5 sec.	145/87	106
		A.N. 30 sec.	125/75	92
		Control	145/87	106
		P.E. early	130/87	100
		P.E. late	190/100	130
8. E.F., 26	Mitral stenosis with pulmonary hypertension	Control	110/70	83
		A.N. 5 sec.	105/75	75
		A.N. 30 sec.	65/70	48
		Control	115/75	88
		P.E. early	105/75	85
		P.E. late	190/100	130

C.F.—Coloured female. E.M.—European male. E.F.—European female. B.M.—Bantu male. B.F.—Bantu female.

Thus, the over-all effect on the pressure differences across the lung in these patients was a slight decline which was due chiefly to the rise in the wedge pressure. This decline averaged 31 per cent (range, 6-78). Cardiac output was found to increase in all patients. It increased less in those with a low resting output than in those with

pressure gradient and makes the differences recorded of greater significance. We can, therefore, interpret the difference between mean pulmonary arterial and mean wedge pressure with a fair degree of confidence.

There is good evidence that the pulmonary arterial wedge pressure accurately reflects the left atrial pressure in cases of mitral stenosis,[4-6] although Murphy[7] has come to the opposite conclusion. As has been previously discussed,[1] amyl nitrite causes very short-lived transitory effects, which makes accurate calculations of

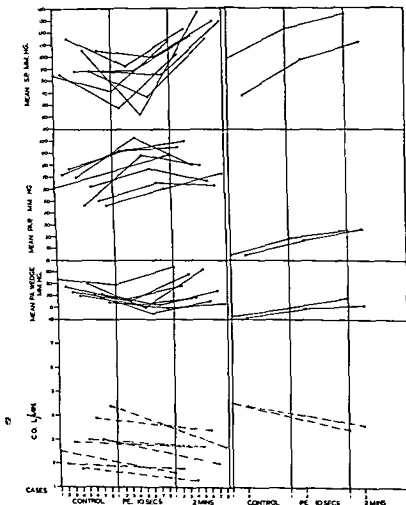


Fig. 3. The effects of the injection of phenylephrine into the pulmonary artery or systemic vein in 8 patients with mitral stenosis and pulmonary hypertension (*in columns on left*) are compared with the results obtained in 2 normal subjects previously studied[1] (*in columns on right*). The systemic pressure falls initially, as does the wedge pressure, at a time when the pulmonary arterial pressure is increasing rapidly. This is interpreted as being due to intense pulmonary vasoconstriction which results in diminished venous return to the left side of the heart. In the later phase the systemic and wedge pressures rise because of systemic vasoconstriction, and the pulmonary arterial pressure remains elevated. As in the normal subjects, cardiac output is decreased after the injection of phenylephrine. The biphasic response of the systemic and wedge pressure is not seen in normal subjects, but also occurred in the subjects with pulmonary hypertension without mitral stenosis, which suggests that in the presence of pulmonary hypertension the pulmonary vasculature is far more reactive than in normal subjects.

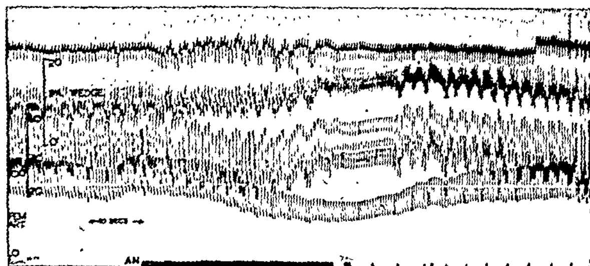


Fig. 2. The pressure record from Patient 8. From above downward are the electrocardiogram, the pulmonary arterial wedge pressure, the pulmonary arterial pressure, and the systemic pressure. Inhalation of amyl nitrite is indicated by the black line at the bottom. The pulmonary arterial pressure starts to fall before any change occurs in wedge pressure, systemic pressure, or heart rate, which suggests a direct effect on the pulmonary resistance vessels. Later, systemic pressure falls acutely, a tachycardia develops, and the wedge pressure begins to rise. Pulmonary arterial pressure now parallels the increase in wedge pressure, so that after 30 seconds it is back to its control level, although the pressure difference across the lungs is still diminished.

sure gradient by flow, was found to be decreased in all cases. This decrease in calculated resistance averaged 45 per cent (range, 31-67).

2. The response to phenylephrine. The data are presented in Table I and Fig. 3. Measurements of pressure were made during the initial phase of maximal effect on the pulmonary arterial pressure and during the late phase of systemic hypertension during the inscription of the dilution curve. When phenylephrine was injected into a peripheral vein or main pulmonary artery, a characteristic biphasic pressure response was obtained in all but one (Patient 4). In the initial phase, immediately after the administration of phenylephrine there was a sharp increase in pulmonary arterial pressure, associated with a brief, sharp drop in pulmonary arterial wedge pressure, and a decrease in systemic pressure, associated with a tachycardia.

After a few seconds a rise in systemic pressure occurred, associated with a bradycardia; wedge pressure rose to the control level or even higher, and pulmonary arterial pressures remained elevated (Fig. 4).

The cardiac output was estimated during the late phase of the response and was invariably found to be decreased. The average decrease in cardiac output was 22 per cent (range, 7-39).

The pressure difference across the lungs as measured at the time when flow was determined was always increased and averaged 52 per cent (range, 18-138).

The combination of an increased pressure difference with a reduction in flow resulted in the calculated vascular resistance being increased in all cases by an average of 105 per cent (range, 21-200).

In Patient 6, a second dose of phenylephrine was injected into the pulmonary artery wedge; after this injection the initial effect was a sharp rise in systemic pressure with bradycardia, which long preceded the increase in pulmonary arterial pressure and the slight drop in wedge pressure (Fig. 5).

Discussion

The reliability of the data. In the presence of severe pulmonary hypertension the pressure differences across the lungs are large, and, therefore, are more easily and accurately measured than in the case of normal pulmonary vascular pressures. The presence of elevated wedge pressures adds to the reliability of the measurement of

the calculated resistance to flow. Thus, the interpretation of calculated resistance in a situation in which pressure, flow, and heart rate are all changing rapidly is extremely difficult. Nonetheless, some discussion on the possible role of changes in vascular tone is necessary.

If it is assumed that the drugs amyl nitrite and phenylephrine have no effect on the viscosity of the blood, on the size of anastomotic vessels, on the opening up of vascular channels previously closed, or on the length of the vascular channels, a significant change in calculated resistance is probably due to a change in the caliber of the vessels. As Burton[11] has pointed out, there are two factors which influence the caliber of resistance vessels. One is the transmural pressure, which can cause vessels to distend or contract passively because of their inherent elasticity, and the other is muscular tone, which can constrict or dilate vessels in response to reflex activity or vasoactive drugs. It can only be concluded that muscular tone has been affected if the possible effect of a change in transmural pressure is taken into account.

The average decrease in pulmonary resistance of 45 per cent which was found after *the inhalation of amyl nitrite* may mean a widening of the caliber of the pulmonary vessels, which could be active or passive. Since this decrease in resistance occurred in the face of elevated pulmonary arterial wedge pressures in 7 of the 8 patients, it is possible that the passive distention of the venous segment of the pulmonary vascular bed alone caused the drop in calculated resistance. However, there are two objections to such a conclusion. In 2 subjects (Patients 5 and 8), a brief drop in pulmonary arterial pressure occurred before any change could be detected in the wedge and systemic pressures and the heart rate (Fig. 2). Since a change in blood flow seems unlikely at this early stage after the inhalation of amyl nitrite, a direct effect of amyl nitrite on the pulmonary resistance vessels in these 2 patients appears to fit the facts best. Furthermore, in the presence of moderate to severe pulmonary hypertension, most of the resistance to flow resides at the level of the arteriole, and it is unlikely that relatively small changes in pressure in the venous segment would materially affect the transmural pressure at the level of the arteriole.

In the light of the preceding considerations the sequence of events which occurs after the inhalation of amyl nitrite is interpreted in the following manner. Inhaled amyl nitrite initially affects the pulmonary resistance vessels to a variable extent, leading to a sharp initial drop in pressure in some subjects. (The means by which the resistance vessels are apparently affected when the drug is absorbed into the pulmonary capillaries remains unexplained.) Thereafter, amyl nitrite reaches the systemic resistance vessels and leads to an acute vasodilatation, with a drop in systemic pressure, tachycardia, and an increased cardiac output. The combined effect of tachycardia and increased venous return elevates the wedge pressure because of the fixed obstruction at the mitral valve. The rise in pulmonary venous pressure may, in turn, lead to a passive rise in pulmonary arterial pressure, which may reach or even exceed the control levels, in spite of some release of pulmonary vasoconstrictor tone.

After the administration of phenylephrine into the pulmonary artery or peripheral vein, there is an initial brisk rise in pulmonary arterial pressure, a slight drop in wedge pressure, and *a drop in systemic pressure* (Fig. 4). This response is quite different from that which occurs in subjects with normal pulmonary arterial pressures, in whom the slight rise in pulmonary arterial pressure is later and, for the most part, secondary to a rise in systemic and wedge pressures.[1] Although cardiac output could not be measured during the brief initial phase, it would seem that the above response can only be explained by an intense vasoconstriction of the pulmonary resistance vessels. This leads to a sharp decrease in venous return to the left side of the heart, with a consequent drop in wedge and systemic pressures. The second phase of the response to phenylephrine consists of a rise in systemic and wedge pressures with bradycardia, and the increase in pulmonary arterial pressure is maintained. The cardiac output during this phase was always decreased by an



Fig. 4. The pressure record from Patient 6. From above downward are the electrocardiogram, the pulmonary arterial pressure, the wedge pressure, and the systemic pressure, the injection of phenylephrine is indicated by the heavy line at the bottom of the tracing. Initially, pulmonary arterial pressure rises while wedge pressure falls, and systemic pressure drops acutely, with resultant tachycardia. After about 30 seconds the systemic pressure rises and a bradycardia occurs, wedge pressure also rises slightly, and the pulmonary arterial pressure remains elevated.

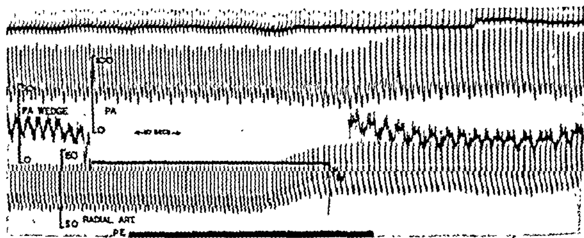


Fig. 5. Pressure records from Patient 6 during the injection of phenylephrine into the wedged catheter. Now the initial effect is a rise in systemic pressure, about 20 seconds later the pulmonary arterial pressure rises and the wedge pressure drops slightly. In this instance the initial effect of phenylephrine has been on the systemic resistance vessels, and the pulmonary effects have occurred later when recirculating phenylephrine reaches the lungs.

flow extremely difficult, since a steady state is not attained. The calculation of cardiac output must, at best, be an approximation under these conditions, even when the dye-dilution technique is used. Nevertheless, from the present data and from data obtained in normal people by us and by other investigators,[8] there seems to be little doubt that nitrites do significantly increase cardiac output, when they drop the systemic pressure acutely.

The data on flow obtained after the administration of phenylephrine are more likely to be reliable, since the effects of phenylephrine persist for 3 to 4 minutes, which makes the estimation of cardiac output by the dilution methods far more acceptable. As in normal people, phenylephrine has the effect of significantly reducing cardiac output.[1,9,10]

The interpretation of changes in calculated vascular resistance. It has been emphasized repeatedly that there is a multiplicity of factors other than tone which can affect

Pulmonary artery		*Wedge*		*CO (L./min.)*	*PVR (units)*	*TSR (units)*	*Heart rate*
S.D	*Mean*	*S.D.*	*Mean*	*(dye)*			
85/40	55	13/11	12	3 1	13 9	33 3	78
80/37	51	10/7	8				
85/40	55	6/3	4	4.8	10 6	12 9	102
84/37	52	15/12	13	3.3	11 8	31 2	78
105/60	75	10/6	7	—	—	—	90
100/40	60	10/8	9	2.6	19 6	44 3	60
115/75	88	—	—	2 8	—	29 6	114
115/70	85						
120/70	87	—	—	3.1	—	23 2	132
115/75	88	—	—	2 7	—	32 6	114
130/80	97	—	—	—	—	—	—
142/70	94	—	—	2 0	—	66 5	54

to the fact that a much weaker concentration of amyl nitrite reaches the pulmonary resistance vessels. By contrast, when there is a large left-to-right shunt, a large concentration of amyl nitrite absorbed via the pulmonary capillary bed is likely to be rapidly shunted into the lungs, which results in a more potent effect on the pulmonary resistance vessels, as previously postulated.[3]

Summary and conclusions

Ten patients with moderate to severe pulmonary hypertension, 8 of whom had severe mitral stenosis, were studied under the conditions of routine cardiac catheterization, and the effects of the inhalation of amyl nitrite and the injection of phenylephrine were observed. Amyl nitrite caused a brisk systemic hypotension with tachycardia and an increase in cardiac output, whereas pulmonary arterial pressures remained relatively unchanged and wedge pressures increased in patients with mitral stenosis. Calculated pulmonary vascular resistance declined by an average of 42 per cent, whereas the decline in systemic resistance averaged 46 per cent.

The significance of the decline in pulmonary vascular resistance is discussed, and it is suggested, but by no means proved, that it is due to a decrease in pulmonary vascular tone.

When phenylephrine was injected into the pulmonary artery or into a systemic vein, the response was characteristically biphasic. Initially, there was a sharp rise in pulmonary arterial pressure, with a fall in wedge and systemic pressures. Later, a rise in systemic and wedge pressures occurred, and the increase in pulmonary arterial pressure was maintained. These effects also occurred in the 2 patients who had no mitral stenosis. In one patient in whom phenylephrine was injected into the wedged catheter, the pressure responses occurred in the reverse order.

Cardiac output which was measured during the later phase was always decreased; the average reduction was 22 per cent. The increase in calculated pulmonary vascular resistance can only indicate a true increase in pulmonary vasoconstriction. The initial effect of the drug was attributed solely to its pulmonary vasoconstrictive effect, whereas a combined systemic and pulmonary response accounted for the late effect. The abnormal vasoconstrictor response to phenylephrine was similar to that found in cases of ventricular septal defect with pulmonary hypertension.

The relative lack of response to amyl nitrite in this group contrasts sharply with the marked pulmonary vasodilator effects found in subjects with ventricular septal defect who have hyperkinetic pulmonary hypertension. Rapid recirculation of amyl nitrite into the pulmonary bed in the latter group may account for the difference

Table II Pressures (mm. Hg)

Patient, Sex, Age	*Diagnosis*	*State*	*Systemic artery*	
			S.D.	*Mean*
1. E.M., 48	Hypertensive corpulmonale	Control	130/90	103
		A.N. 5 sec.	100/70	80
		A.N. 30 sec.	85/50	62
		Control	130/90	103
		P.E. early	110/90	97
		P.E. late	165/90	115
2. E.M., 22	Idiopathic pulmonary hypertension	Control	100/75	83
		A.N. 5 sec.	100/70	80
		A.N. 30 sec.	85/65	72
		Control	105/80	88
		P.E. early	105/75	85
		P.E. late	170/115	133

average of 22 per cent. At this time, the pressure gradient across the lungs was increased by an average of 52 per cent. The increase in calculated vascular resistance must reflect a true increase in vascular tone since the intraluminal pressure at the arteriolar end of the vascular bed is increased and at the venous end it is either slightly increased or unchanged.

In one patient (Patient 6), phenylephrine was injected into the wedged catheter so that its initial effect would be on the systemic circuit (Fig. 5). The initial response then was a rise in systemic pressure with bradycardia followed by a rise in pulmonary arterial pressure and a drop in wedge pressure. This difference is adequately explained by the fact that phenylephrine has its initial effect on the systemic circuit, and subsequently affects the pulmonary vasculature.

Studies[4] in patients with ventricular septal defects who had large left-to-right shunts and associated pulmonary hypertension have provided evidence for an unusual responsiveness of the pulmonary resistance vessels to these drugs. It seemed likely that amyl nitrite caused a greater fall in pulmonary than in systemic resistance, and that phenylephrine had the reverse effect. In our patients who had mitral stenosis and an intact circulatory pathway a marked reactivity of the pulmonary vascular bed to phenylephrine has been demonstrated, but the response to amyl nitrite has been rather disappointing and the evidence for a release of vasomotor tone inconclusive.

In order to determine whether the failure of the pulmonary arterial pressure to fall after amyl nitrite was due to the presence of mitral stenosis in these patients, two patients without mitral stenosis were studied (Table II). One had pulmonary hypertensive cor pulmonale, and the other had idiopathic pulmonary hypertension; and in both the severity of the pulmonary hypertension was comparable to that of the patients with mitral stenosis. A marked pulmonary vasoactive response to phenylephrine was demonstrated in both cases. However, as in most of the cases of mitral stenosis, amyl nitrite had virtually no effect on the pulmonary arterial pressure.

It seems, therefore, that amyl nitrite has strikingly different effects on the pulmonary vascular bed in patients with a left-to-right shunt and in those with intact circulatory pathways. It seems unlikely that the lack of effect in the latter group can be ascribed to fixed organic obliterative vascular changes, since other studies have repeatedly demonstrated[12] a release of tone in the lung vessels in cases of mitral stenosis, and our results with phenylephrine clearly indicate that the vessels can constrict.

Thus, it is suggested that the relative lack of response to amyl nitrite in cases without a left-to-right shunt may be due

Table I. Cardiac and renal hemodynamic parameters from all procedures

Case number, Age, Body surface area (M.²)		Pulse rate	Mean arterial pressure	Cardiac index	Total peripheral resistance	Renal blood flow	Renal resistance (× 10³)	RBF/CO ratio
I	Control	60	134	2 69	2,140	550	25 8	.110
49	Treated 1 wk.	55	97	4 56	910	560	18 4	.066
1.86	Treated 6 wk.	54	97	3 22	1,290	492	21.0	.082
II	Control	71	155	2 18	3,020	560	29.5	.136
49	Treated 1 wk.	56	152	2 51	2,590	312	51 8	.066
1.88	Treated 6 wk.	56	145	2 63	2,340	278	55.9	056
III	Control	60	120	3 93	1,620	450	28.3	.078
65	Treated 1 wk.	57	122	4 60	1,415	562	23.1	.081
1 50	Treated 6 wk.	51	88	3.43	1,400	448	21 0	086
IV	Control	61	162	2 31	2,940	510	33.9	.116
47	Treated 1 wk.	58	94	2 21	1,780	447	22 4	.106
1 90	Treated 6 wk.	58	100	2 57	1,630	508	20 9	.104
V	Control A	90	107	3 10	1,230	442	25 8	.065
47	Treated 1 wk.	64	97	3 77	935	543	19 0	065
2.20	Control B	77	123	2 52	1,760	900	14 6	.162
					1,490	1,151	14 2	154
VI	Control	75	140	3 12				
42					1,030	1,310	8 0	.172
2.40	Treated 6 wk.	65	98	3 16				
VII	Control	65	165	2 39	3,640	517	42 2	.115
36	Treated 1 wk.	60	132	2 61	2,500	240	58 6	060
1.52								
VIII	Control	67	160	2 65	2,460	646	26 3	.124
32	Treated 1 wk.	59	115	3 00	1,516	824	14 5	139
1 96	Treated 6 wk.	56	100	3 20	1,270	766	13 9	.121
	Mean control (Standard deviation)	67 (6 7)	145 (18)	2 72 (0 38)	2,384 (759)	661 (213)	26 8 (8 7)	
	Mean treated 1 wk. (Probability)	58 (3>p> 1)	115 (2>p> 1)	3 32 (2>p> 1)	1,662 (.5>p> 3)	498 (7>p> 5)	29 6 (8>p> 7)	
	Mean treated 6 wk. (Probability)	57 (2>p> 1)	105 (p 05)	3 01 (5>p> 3)	1,492 (3>p> 2)	634 (p 9)	23 5 (8>p>.7)	

Units are as indicated in text under *Calculations*. Mean values are furnished in the lower section of the table, with standard deviation of control measurements and statistical probability of treated values.

brated syringe was used for injection of indocyanine green in all instances. Dye-dilution curves were recorded continuously from the radial artery through a photoelectric cuvette. Direct arterial pressure tracings with electrically integrated mean pressure were obtained before and after each dye-dilution curve, with an Electronics for Medicine photographic record. In 4 cases, determinations of blood volume with radioactive iodinated serum albumin (RISA) were performed during the sampling period, employing a 15-minute dilution period.

Oral reserpine therapy, augmented in 2 cases by intravenous reserpine, was administered after the initial procedure. The drug was increased daily in increments of 2.0 mg., until a hypotensive response was obtained. At the end of 1 week, hemodynamic measurements were repeated in the manner described. The average daily dose of reserpine at the end of the first week of treatment was 6.0 mg. The patients were discharged after the second procedure and followed for 6 weeks in the outpatient facility. During this interval, reserpine was the only medication allowed (average maintenance dose, 4.0 mg. daily). Patients were readmitted at the termination of the 6-week period of treatment, and the hemodynamic studies were carried out for the third and final time.

Calculation and analytical methods

Para-aminohippuric acid was determined by the method of Smith.[1] Cardiac output was derived from the dye-dilution curves by the method of Hamilton,[2-4] using multiple calibration points and replotting on semilogarithmic paper. The formulas used for calculation are shown below.

Results

The hemodynamic data obtained are tabulated in Table I. A definite hypotensive response was obtained in 7 of the 8 patients. The average daily dose of reserpine employed was 6.0 mg. in divided doses (range, 2.0 to 20.0 mg. daily). The patient who did not respond satisfactorily to the drug (Case II) had a 40-year history of hypertension, persistant albuminuria, and a blood urea nitrogen of 22 mg. per cent.

The procedure outlined was deviated from in three instances. One patient (Case V) experienced a hypotensive reaction during the initial control period. He was allowed, therefore, to return to the control

$$\text{Cardiac index (L./min./M.}^2\text{)} = \frac{\text{Cardiac output (L./min.)}}{\text{Body surface area (M.}^2\text{)}}$$

$$\text{Total peripheral resistance (dynes-sec.-cm.}^{-5}\text{)} = \frac{\text{Mean arterial pressure} \times 1{,}332 \times 60}{\text{Cardiac output (ml./min.)}}$$

$$\text{Mean circulation time (dye-dilution technique)} = \frac{(C \times t)}{t}$$

$$\text{Pulmonary blood volume} = \frac{\text{Cardiac output (ml./min.)} \times \text{Mean circulation time}}{60}$$

$$\text{Stroke volume} = \frac{\text{Cardiac output (ml./min.)}}{\text{Heart rate}}$$

$$\text{Renal resistance (dynes-sec.-cm.}^{-5}\text{)} = \frac{\text{Mean arterial pressure} \times 1{,}332 \times 60}{\text{Renal blood flow}}$$

$$\text{Renal blood flow} = \frac{\text{Renal plasma flow (PAH clearance)}}{\text{Hematocrit} - 1}$$

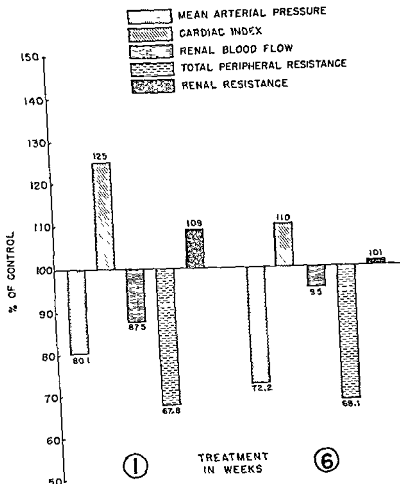


Fig. 1. Composite parameters of cardiac and renal hemodynamics for the entire study group after 1 and 6 weeks of reserpine therapy. Measurements are expressed as the averaged per cents of control values Control values represent 100 per cent.

the renal blood flow. Cardiac output is noticeably increased as a result of the tachycardia induced. The long-term studies of Vander Kolk[9] have demonstrated that the increase in the renal blood flow is not so great after the initial period of treatment; a 6 per cent over-all increase was observed.

Observations on the cardiorenal effects of reserpine in dogs are reported by Moyer,[10-11] who noted that both cardiac output and renal blood flow were relatively unchanged by reserpine therapy. Redisch and coworkers[12] report simultaneously determined cardiac output and renal clearance of para-aminohippuric acid in human beings after acute intravenous administration of reserpine. They found that the delayed hypotension induced is associated with little or no change in cardiac output, a late and transient rise in renal blood flow, and a slight increase in pulse rate.

Although this series contains a limited number of observations, which have questionable statistical significance in magnitude, certain consistencies in the measurements are apparent. All patients at 1 and 6 weeks of treatment showed a reduction in pulse rate which averaged 15 per cent of the control rates. A reduction in peripheral resistance was found in all patients, including one in whom the hypotensive response was unsatisfactory. A reduction in mean arterial pressure was effected initially in 7 of the 8 patients, with a concomitant increase in the cardiac output and cardiac index. After 6 weeks of therapy the mean

state (Control B) 2 weeks before the final determination of simultaneous cardiac output and renal blood flow. Figures given under the heading of *Control A* in Table I were obtained during the initial hypotensive reaction. Figures listed under *Control B* are those used as control values for analysis. Data from Case VI on the second procedure were technically unsatisfactory. A third patient (Case VII) withdrew from the study before the final procedure could be performed.

The data presented in Table I as absolute measurements are summarized in Fig. 1 in terms of the averaged per cents of control values after 1 and 6 weeks of therapy. There was an initial increase in cardiac index, except in Case IV. This increase averaged 25 per cent for all patients. After 6 weeks of treatment the cardiac output had returned toward control levels, with an average increase of 10.0 per cent.

At 1 week, mean arterial pressure was reduced in all except Case III; the average reduction was 19.9 per cent of control. After 6 weeks of treatment a reduction in mean arterial pressure was observed in all cases and averaged 27.7 per cent of control.

In all cases the calculated total peripheral resistance decreased both initially and at 6 weeks. This decrease averaged 32.2 per cent of control at 1 week, and 31.0 per cent after 6 weeks of therapy.

Renal blood flow decreased in 4 and increased in 3 patients at 1 week. The overall average decrease was 12.5 per cent. After 6 weeks of therapy, renal blood flow was increased in only 2 of the 6 patients in whom it was determined. When all cases are considered, renal blood flow was reduced an average of 5.0 per cent of control level after 6 weeks.

The calculated renal resistance increased initially in 3 of 7 patients. The average for all patients was an increase of 9 per cent. After 6 weeks of treatment the average calculated renal resistance returned to the control level.

The calculated mean circulation time was slightly reduced (average, 7.2 per cent) in 6 and unchanged in 2 patients. Pulmonary blood volume increased in 6 patients by an average of 21.5 per cent after 1 week of therapy. After 6 weeks of therapy, 3 patients showed an average increase in pulmonary blood volume of 17 per cent. Two patients (Cases III, IV) had a reduction in pulmonary blood volume of 10 per cent, and in another patient (Case VI) it was unchanged.

Studies of blood volume in 4 of the 8 patients showed no change in the plasma volumes before and after treatment with reserpine. A slight increase in control plasma volume, which remained unchanged during therapy, was observed in all cases.

Side reactions to reserpine were noted in all 8 patients studied. In the order of their frequency of occurrence, these reactions were: sleepiness and lethargy (8 patients), undesirable personality changes (6 patients), hypersalivation (5 patients), sexual impotence (all 4 male patients), nasal stuffiness (2 patients), weakness of the legs (2 patients), agitation (2 patients), nightmares (2 patients), excessive appetite (2 patients), blurred vision (1 patient).

Discussion

Simultaneous cardiac and renal hemodynamic studies have been reported in the evaluation of a few commonly used antihypertensive agents, such as the ganglionic-blocking drugs, 1-hydrazinophthalazine, and reserpine. Reserpine has been the least studied in this manner. In part, this paucity of data on reserpine is based on the consistently rapid and good response elicited by the ganglionic-blocking agents which facilitates study. The widespread use of rauwolfia alkaloids in the treatment of essential hypertension makes adequate and reproducible physiologic data on these drugs of interest.

Smith and Hoobler[4] have demonstrated that the antihypertensive effect of the ganglionic-blocking drugs results in part from a reduction in cardiac output, with little or no change in the peripheral resistance. The renal blood flow and glomerular filtration rate are dramatically reduced with these agents, as shown by Moyer and associates,[5,6] and Ford and associates.[7] A slight increase in renal resistance was effected by the blocking agent in the study of Moyer.[6]

In contrast, Rose and co-workers[8] and Vander Kolk and associates[9] showed that 1-hydrazinophthalazine reduces both the total peripheral vascular resistance and the renal resistance, resulting in an increase in

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arterial pressure showed a continued reduction, whereas the cardiac index returned toward control levels. Associated with the increase in cardiac output was a slight reduction in mean circulation time and an increase in the pulmonary blood volume. There was no increase in venous pressure. The RISA-determined blood volume remained stationary. These data indicate that the hypotensive action of reserpine was due to a reduction in vascular tone without a reduction in cardiac output, peripheral pooling of blood, or decreased circulating blood volume.

The renal hemodynamic and functional changes were less consistent and bear no statistical significance. There was only a slight over-all decrease in the renal blood flow, which varied throughout the study group. At the end of 6 weeks of therapy an over-all mild reduction in renal blood flow had occurred, despite the return of renal resistance to control levels.

When viewed together, the data indicate that hypotension induced with reserpine results in satisfactory control of the peripheral resistance and the mean blood pressure, without compromising the cardiac output or peripheral circulation. The renal circulation in acute therapy is relatively diminished; however, it returns toward control levels on prolonged therapy.

The distressing nature of the side effects has been mentioned by Quetsch[13] as sufficient to warrant caution in administering this drug. It became necessary to discontinue reserpine therapy in 3 patients at the end of the study period because of agitation and depression. In these 3 patients there seemed to be no level consistent with a satisfactory hypotensive response which was not associated with side effects. The remainder of the patients continued on established dosages (average, 3.2 mg. daily) after the study period. Because of the control nature of the study, no attempt was made to interfere with the development of side effects to reserpine.

Summary

Cardiac and renal hemodynamic data are presented on 8 patients treated with reserpine. These data are equated to control parameters determined at a time before the treatment was employed. Reserpine therapy in these patients produced a sustained reduction in peripheral resistance, mean arterial pressure, and pulse rate, with an increase in cardiac output. Renal blood flow was decreased early in therapy but returned to control levels within 6 weeks. Renal resistance was usually reduced by reserpine therapy. A brief discussion of similar measurements with other antihypertensive drugs was presented.

Appreciation is hereby expressed to Ciba Pharmaceutical Products, Inc., for supplying the reserpine (Serpasil) used in this study.

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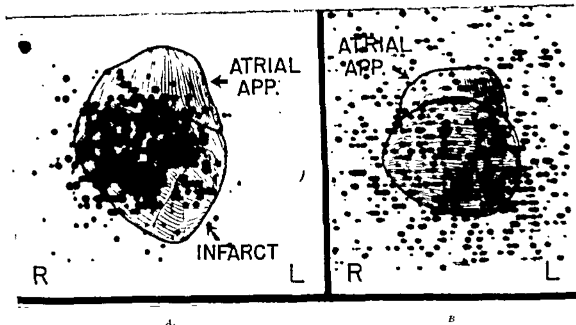


Fig. 1. Photoscintigrams of isolated hearts of 2 dogs that had received $Rb^{86}Cl$. In this and all subsequent figures, all outlines drawn as heavy black lines on the photoscintigrams were obtained by direct projection (see text). Only the faint shading to indicate cardiac tissue has been added by the illustrator. A, Heart from a dog with a myocardial infarct in the indicated area, confirmed histologically. B, Heart from a control dog. The infarct is seen as a "cold" area. The lower concentration of Rb^{86} in this area was subsequently confirmed by direct counting of radioactivity in tissue samples.

closed in layers. Nine dogs, which ranged in weight from 7.0 to 12.2 kilograms, survived the operation 24 hours or more. The other dog is not considered further in this report.

Sham operations. As controls, 5 dogs, which ranged in weight from 7.6 to 12.4 kilograms, were subjected to operation in the same manner as the previous group, except that no ligature was placed around the coronary artery after the pericardium had been opened.

Scanning. One to 21 days after operation each dog received 700 μc of Hg^{203}-chlormerodrin* intravenously. Scanning began 40 minutes to 25 hours after administration of the labeled compound. In preparation for scanning, each dog was again anesthetized by intravenous injection of sodium pentobarbital and placed in the supine position on a table. The legs of the dog were extended and firmly tied. An area which extended from about 1 cm. below the xiphoid to about 2 cm. below the cephalic border of the manubrium sterni, and which extended beyond the lateral thoracic walls on each side, was then scanned with a photoscanner* equipped with a 3 by 2-inch crystal and a 19-hole focusing collimator. The edge of the collimator was placed about 1 cm. above the anterior chest wall at the level of the sternum. Scanning speed was usually 16 cm. per minute. The contrast adjustment of the scanner was set at the "15" position, a setting designed for sharp contrast. Before every scan, the probe was repeatedly moved manually over the entire precordial area until the spot of greatest radioactivity was found. The voltage of the scanner was then adjusted to yield maximum blackness of the photoscintigram over this area.

At the conclusion of the scan, the animal was left in position and sacrificed by intraperitoneal injection of 10 to 20 ml. of a solution of sodium pentobarbital in isopropyl alcohol and propylene glycol.†

*Abbott Laboratories, Oak Ridge, Tenn.; E. R. Squibb and Sons, Cleveland, Ohio.

*Picker Magnascanner, Picker X-Ray Corporation, White Plains, N. Y.

†"Lethal" solution, Haver-Lockhart Laboratories, Kansas City, Mo.

The detection of experimental myocardial infarcts by photoscanning

A preliminary report

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The heart shadow as visualized roentgenographically is the result of superimposition of several tissues, including the blood content of the heart. Other roentgenographic and radioisotopic techniques used to visualize the heart show only its cavities. The studies of Burch and his associates,[1,2] which indicated rapid uptake of rubidium-86 by the myocardium, suggested the possibility of demonstrating the myocardium by photoscanning after administration of this radioisotope. Our previous work[3] confirmed the feasibility of demonstrating the myocardium of the beating heart of living dogs by this technique. Furthermore, in photoscintigrams of the excised hearts of dogs previously subjected to coronary artery ligation, the area of infarction was demonstrable as a "cold" area of relatively decreased uptake of rubidium-86 (Fig. 1).

The successful use of mercury-203-labeled chlormerodrin (Neohydrin) in the demonstration of brain tumors by photoscanning[4-6] suggested the possible use of this compound to demonstrate myocardial infarcts as "hot" areas of relatively increased concentration of radioisotope in photoscintigrams of the heart. The present communication describes experiments designed to explore this possibility.

Methods

*Coronary artery ligations.** Ten mongrel dogs were anesthetized with sodium pentobarbital, given intravenously. While respiration was maintained by a pump connected to an intratracheal catheter, the heart was exposed through a left lateral thoracic incision, employing subperiosteal resection of a portion of one rib. The pericardium was opened and a ligature passed around the anterior descending branch of the left coronary artery just below the bifurcation. After a loose single knot had been tied in the ligature, the shaft of a No. 20 needle was placed in the loop parallel to the artery and the ligature drawn tight. This incomplete occlusion of the artery was allowed to persist for about 10 minutes. The needle was then withdrawn, the ligature tightened down on the artery to occlude it completely, and the knot completed. The incision was then

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Results

Photoscintigrams. The results in a dog with a frank infarct are shown in Fig. 2. In the living dog a "hot" area of increased concentration of isotope was seen in the area of left ventricle supplied by the ligated artery (Fig. 2,*A*). The scan of the excised heart, emptied of blood, confirmed the presence of this "hot" area (Fig. 2,*B*).

In the scan of a sham-operated animal (Fig. 3, *A* and *B*), no such area of increased concentration of isotope appeared. Although further discussion of scanning technology is beyond the scope of this paper, it should be noted that the method used here to set the scanner voltage and contrast (see Methods) produces a scan in which the criterion of normality or abnormality is *contrast*, not film density itself. If the distribution of isotope throughout the ventricles is relatively even (normal state), the scan shows considerable density throughout but no area of contrast. If there is very heavy concentration in one area (abnormal state), the scan shows one area of heavy density and little density elsewhere.

One finding in some scans of control dogs had a superficial resemblance to an infarct. This finding was a spindle-shaped area of moderately increased density on the right side of the heart, extending from the diaphragm toward and sometimes beyond the base of the heart. Such an area was seen in 2 of 7 dogs scanned from 2¼ to 3½ hours after injection of the isotope, and in 1 of the 3 dogs scanned at the 7 to 7¾-hour interval, but not in any of the dogs scanned on the day after injection. It was completely absent from all scans of isolated hearts emptied of blood. This indicated conclusively that the "spindle" did not have its origin in the myocardium; superimposition of blood in the caval veins upon the blood of the heart probably accounted for the density. Its characteristic shape, position, and extent made it distinguishable from an infarct.

Areas of "ischemia" without frank infarction (see below) were also clearly detectable on scans (Fig. 4, *A* and *B*). Thus, scans of "ligated" dogs were clearly different from those of sham-operated control dogs; in the former the areas of interrupted blood supply appeared positive in the presence or absence of frank myocardial necrosis.

Tissue studies

LEFT VENTRICLE. Since all coronary artery ligations were performed on the anterior

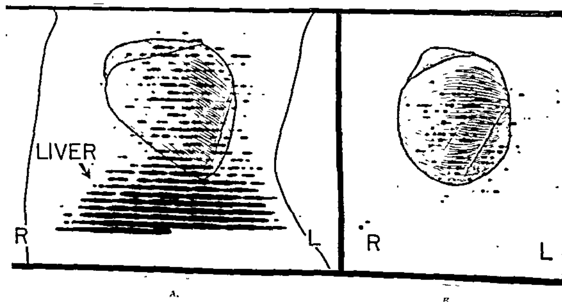


Fig. 3. Photoscintigrams of the heart of a dog (Dog 4, Table I) which had received Hg^{203}-chlormerodrin after a sham operation. The heart shows a diffuse, even concentration of the isotope, with no well-localized "hot" area standing out in sharp contrast. The even distribution of Hg^{203} was subsequently confirmed by direct counting of radioactivity in tissue samples.

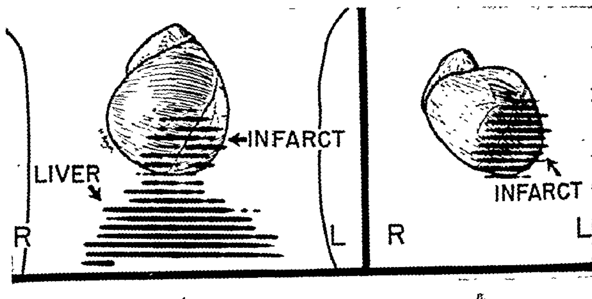


Fig. 2. Photoscintigrams of the heart of a dog (Dog 2, Table I) which had received Hg^{203}-chlormerodrin after coronary artery ligation with myocardial infarction. In this and subsequent figures, *A* shows the photoscintigram obtained in the living dog, the projections of heart, body wall, coronary artery, and atrioventricular sulcus were added after death. *B* shows the same heart, rescanned after removal from the dog. The "hot" area seen in the heart of the living dog and in the same isolated heart corresponds to the area of infarction, demonstrated histologically. The localization of Hg^{203} in this area was subsequently confirmed by direct counting of radioactivity in tissue samples.

With the aid of a narrow light beam attached to the collimator, the probe was centered over the xiphoid and over the cephalic tip of the sternum, and their precise positions were projected on the dot scan which had been obtained simultaneously with the photoscan.

The heart was then fixed in position by inserting several (usually 3) long, sharp steel needles through the anterior chest wall in such a way as to transfix the heart. The points of the needles were driven firmly into the posterior thoracic wall of the dog. Without any change in the position of the carcass or needles, the central portion of the anterior chest wall was dissected free and removed. After the pericardium had been reflected, the entire outline of the exposed heart and the position of the anterior descending branch of the left coronary artery were projected onto the dot scan. After development of the photoscan, it was superimposed on the dot scan, and the markings on the latter were transferred to the former.

The heart was then removed and carefully freed of all blood by repeated washings with isotonic saline solution. In most instances this was facilitated by an incision in each lateral margin of the heart, opening the cavities of the ventricles. After the heart had been washed free of blood, the incisions were closed by sutures, and the isolated heart was rescanned with appropriate readjustment of scanning factors and collimator distance.

Tissue studies. Samples (35 mg. to 2.8 Gm.) of left ventricle, right ventricle, atrium, and various other tissues (Table I) were taken, and their radioactivity was determined in a well-type scintillation counter. Samples of left ventricle regularly included some from the area supplied by the anterior descending branch of the left coronary artery and others from areas in the posterior wall of the left ventricle supplied by the nonligated circumflex branch. All samples of left ventricle were placed in formalin after counting and examined histologically by a member of the staff of the Department of Pathology* who was not informed of the results of scanning or tissue counting.

*The valuable services of Dr. Robert Schmidt and Dr. Robert Hendrix are gratefully acknowledged.

as the standard of comparison:

$$R = \frac{\frac{\Sigma x}{n}}{B}$$

where R = the relative concentration of Hg^{203} in any tissue of a given dog; x = the concentration of Hg^{203} in a single sample, expressed as counts per minute per gram; n = the number of samples; B = the concentration of Hg^{203} in the same dog's blood, expressed as counts per minute per gram.

In Table II, the relative concentrations of Hg^{203} in left ventricle are compared. A significant difference ($0.0125 < p < 0.025$) was found by the "t" test between "anterior left ventricle, ligated" and "posterior left ventricle, normal" in the dogs subjected to ligation. No significant difference was found between "anterior left ventricle, normal" and "posterior left ventricle, normal" in the sham-operated dogs. Coronary artery ligation thus caused a significantly higher relative concentration of Hg^{203} in the area supplied by the ligated branch.

But the data in Table II show only a difference between normal areas and those supplied by a ligated branch. Since, as noted previously, *both* infarcts and "ischemic" areas had high concentrations of Hg^{203}, the question of a difference *between* infarct and "ischemia" remains. In all 4 dogs (Dogs 6, 7, 8, and 13) in which samples in both abnormal subclasses were obtained, the relative concentration of Hg^{203} was found to be higher in infarcts than in "ischemic" samples. Moreover, since Dogs 1 and 2 were both sacrificed 2¼ hours after injection, comparison of the "ischemic" area in Dog 1 with the infarct in Dog 2 is germane. An analogous situation obtains with Dogs 10 and 9. In both instances the relative concentration of Hg^{203} was again found to be higher in infarcts than in "ischemic" samples. The data, therefore, suggest a somewhat higher relative concentration of Hg^{203} *in infarcts* than in "ischemic" areas.

Right ventricle. The concentration of Hg^{203} did not differ significantly from that in normal left ventricle.

Atrium. The relative concentration of Hg^{203} was higher than that in posterior (normal) left ventricle in 10 of 13 dogs. This difference is significant ($p < 0.05$).

Other tissues. Absolute rather than relative concentrations are used here to facilitate comparison of concentrations of Hg^{203} among the normal tissues, including blood, of each individual dog. In each dog the concentration of Hg^{203} in *liver* was greater than that in any other normal tissue studied, including blood. The hepatic concentration was always higher than that in infarcts, except in Dogs 2 and 6. Next to liver, the concentration of Hg^{203} in *lung* was higher than that in other normal solid tissues, except for atrium and rib in one dog each. The concentration of Hg^{203} in lung was less than in blood in only 4 dogs, all of which were sacrificed before 8 hours. The pulmonary concentration of Hg^{203} was less than the concentration in infarcts in each dog, except Dog 9, but greater than that in "ischemic" samples in 5 of 7 dogs.

Rib showed a concentration of Hg^{203} higher than that in normal left ventricle in 6 dogs, and a concentration higher than that in blood in 4, including 3 sacrificed at 23 to 26 hours. The concentration of Hg^{203} in rib was always lower than the mean concentration in abnormal left ventricle of the same dog.

Fat and *muscle* had generally low concentrations of Hg^{203}. In Dog 7, fat had a higher concentration of Hg^{203} than did "ischemic" left ventricle; otherwise, fat and muscle had a lower concentration of Hg^{203} than did abnormal left ventricle in each ligated dog.

Discussion

Photoscintigrams. These studies show that a myocardial infarct in the beating heart of a living animal can be demonstrated through the intact chest wall. The correctness of the identification of the infarcts in vivo has been confirmed in four ways: projection of the outline of the heart in situ on the scan obtained in vivo; redemonstration of positive areas on rescans of excised, emptied hearts; demonstration of increased concentration of Hg^{203} by direct counting of radioactivity in histologically confirmed lesions; and negative results in similarly studied controls subjected to a sham operation complete in every detail except for actual

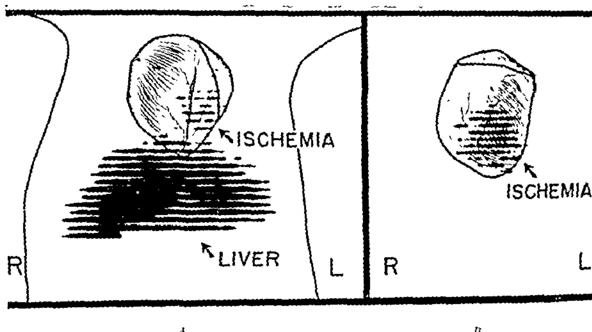


Fig. 4. Photoscintigrams of the heart of a dog (Dog 1, Table I) which had received Hg^{203}-chlormerodrin after coronary artery ligation without myocardial infarction. The "hot" area seen in the heart of the living dog and in the same isolated heart is restricted to the portion of left ventricle supplied by the ligated branch of the coronary artery. The localization of Hg^{203} in this area was subsequently confirmed by direct counting of radioactivity in tissue samples.

descending branch, all samples from the area supplied by this branch, i.e., the anterior ventricular wall, were classified as "anterior left ventricle, ligated" (see below) in Table I. Samples from the area supplied by the nonligated branch, i.e., the posterior ventricular wall, were classified as "posterior, left ventricle, normal" in Table I. Samples from the anterior and posterior ventricular walls of sham-operated dogs were classified as "anterior left ventricle, normal" and "posterior left ventricle, normal," respectively.

All samples classified as "normal" were found to be normal on histologic examination, except for occasional evidence of congestion, which was never marked or associated with any other definite histologic abnormality.

All samples which showed frank necrosis histologically came from the "anterior left ventricle, ligated" group. All other samples from the "anterior left ventricle, ligated" group, i.e., those that did not show actual necrosis, were arbitrarily classified as "ischemic." The justification for this subclassification will be discussed below. Some "ischemic" samples showed marked histologic abnormality, even though frank necrosis was absent, whereas others showed no clear histologic abnormality.

The data in Table I suggest little variation in the concentration of Hg^{203} within any individual normal left ventricle, with the unexplained exception of Dog 13. All samples of infarct showed a higher concentration of Hg^{203} than did all normal left ventricular samples from their respective hearts. Fifteen of the 16 "ischemic" samples showed a higher concentration of Hg^{203} than did all normal left ventricular samples from their respective hearts, even in Dog 13. Among "ischemic" samples no definite correlation was noted between the concentration of Hg^{203} and the degree of histologic change.

The variation in interval between injection of tracer and sacrifice of the animal made it desirable to compare relative as well as absolute concentrations of Hg^{203}. In view of the clear inverse relation between the interval and the concentration of Hg^{203} in whole blood, the latter was used

6. Coronary artery ligation 10 days previously	2¾	16,800 18,500	—	21,000	122,000 124,000 160,000	22,100	15,800	66,800	135,000	72,700	12,400	8,000	13,500	10,200
7. Coronary artery ligation 21 days previously	3½	12,900 13,600	—	17,700	36,200 60,000 60,600	12,900	16,200	41,800	133,000	49,100	13,800	8,680	8,560	25,200
8. Coronary artery ligation 1 day previously	7	8,820 9,050	—	41,600	44,500 52,000	9,310	12,200	18,700	66,400	43,600	9,350	4,400	8,620	9,590
9. Coronary artery ligation 4 days previously	7½	9,330 9,580	—	—	34,300 40,000 44,700	9,820	13,300	30,300	104,000	59,500	2,810	4,730	5,490	4,740
10. Coronary artery ligation 3 days previously	7¾	9,360	—	8,990 9,410 43,100	—	8,020	60,000	20,800	182,000	12,600	6,700	3,770	4,750	3,060
11. Sham operation 1 day previously	23¼	3,690 4,180	3,840 4,180 4,330	—	—	3,210	6,010	6,990	90,600	17,000	9,530	2,060	3,620	3,880
12. Coronary artery ligation 4 days previously	24¼	5,800 6,360	—	6,560 6,890 26,700	—	6,150	6,930	6,660	71,600	29,500	6,720	3,180	4,790	2,850
13. Coronary artery ligation 1 day previously	25¾	9,940 36,900	—	59,000	42,500 86,000	9,450	12,000	5,170	96,900	32,800	5,770	3,780	6,860	3,830
14. Sham operation 1 days previously	26	7,050 7,260	7,120 7,320 7,480	—	—	7,970	10,900	5,630	101,000	27,800	2,710	3,540	5,050	3,890

*See text.
†Atrial tissue was taken from the atrial appendage.
‡Where more than one count is reported, each refers to a separate sample.

Table I. Distribution of Hg^{203} in dog tissues

Dog number	Status	Time between injection of Hg^{203} and sacrifice (hr.)	Concentration of Hg^{203} (c.p.m./Gm. wet weight): Heart: Left ventricle: Posterior (normal)*	Heart: Left ventricle: Anterior (normal)*	Heart: Left ventricle: Anterior (ligated): Ischemic (no infarct)*	Heart: Left ventricle: Anterior (ligated): Infarct*	Heart: Right ventricle	Heart: Atrium	Blood	Liver	Lung	Rib	Muscle: Intercostal	Muscle: Diaphragmatic	Fat
1.	Coronary artery ligation 1 day previously	21¼	19,000‡ 16,700	—	51,300 53,100 97,000 119,000 139,000 161,000	—	19,300	30,900	118,000	259,000	107,000	16,900	7,700	9,800	2,100
2.	Coronary artery ligation 4 days previously	21¾	31,200 32,300	—	—	315,000 377,000 397,000 189,000	39,100	41,700	137,000	211,000	132,000	23,000	20,000	21,300	16,700
3.	Sham operation 4 days previously	21¾	—	24,800 25,700 26,400	—	—	22,700	26,700	90,800	310,000	93,200	98,100	15,600	21,700	16,200
4.	Sham operation 1 day previously	23½	9,140 9,590	8,420 9,280 9,600 10,600	—	—	9,150	14,600	29,800	76,800	60,000	13,800	4,680	7,030	7,170
5.	Sham operation 11 days previously	23½	21,300 31,000	22,300 23,200 23,800 24,200 26,300	—	—	22,600	16,300	91,900	112,000	91,700	17,600	10,800	13,800	12,200

one respect, i.e., the "spindle" artefact appeared in some scans made at intervals up to 8 hours after injection but not in any made at later times. Nevertheless, except for this one suggested difference, our photoscintigrams to date do not clearly indicate that those made at 2 hours are generally inferior for the detection of infarcts or "ischemia" to those made at 24 hours. It is possible that the trend toward higher ratios of concentrations of Hg^{203} in abnormal left ventricle to concentrations of Hg^{203} in normal left ventricle at the early intervals offered an advantage to early scans, offsetting the disadvantage just discussed. Because the number of dogs scanned at each interval was not large, judgment as to the best time for scanning must be reserved.

Under optimal conditions of scanning, what percentage of ligated dogs would yield diagnostic scans? Since we do not claim to have established optimal conditions at present, this question *cannot* be answered with any certainty. However, previous experiences with scans of other organs, using the same type of photoscanner employed in the present study, suggest that the minimal detectable difference between two concentrations of radioactivity, under optimal conditions, is roughly 15 per cent. Seven of the 9 dogs ligated had minimum concentrations of Hg^{203} in infarcts or "ischemic" areas that were $\geq$ 15 per cent above the maximum concentrations in normal left ventricle.

Tissue studies. The relation of concentrations of Hg^{203} in tissue to the results seen in the photoscintigrams has been discussed above.

A possible relationship between the age of the infarct and the concentration of Hg^{203} was sought by making comparisons among dogs sacrificed at the same interval after injection of the tracer. No such relation was apparent. A separate series of experiments designed to clarify this single point might, of course, demonstrate such a difference, especially if infarcts more than 21 days old were studied.

Borghgraef and Pitts[7] and Kessler, Lozano and Pitts[8] reported data on several normal dogs sacrificed 2 to 3 hours after injection of Hg^{203}-chlormerodrin. The mean ratios of concentration of Hg^{203} in tissue to concentration of Hg^{203} in whole blood, in normal heart, liver, lung, and muscle of Dogs 1-7 in the present study, agree very closely with the mean ratios, concentration of Hg^{203} in tissue to concentration of Hg^{203} in plasma, for these same tissues, respectively, calculated from the combined data of these two other reports.

The reason for the localization of Hg^{203} in infarcts is uncertain and deserves further study. Dogs in which only the coronary artery was ligated (the patency of the accompanying veins was carefully preserved and later confirmed at autopsy) showed concentrations of Hg^{203} in their infarcts as high as those in dogs in which both artery and accompanying venous branches were ligated. It may seem surprising at first that an infarct produces a "hot" area with Hg^{203}-chlormerodrin. One might expect an area of diminished blood supply to be "cold." But it must be stressed that coronary occlusion does not result in total obliteration of all blood supply to the distal area, else all coronary occlusions would invariably lead to irreparable necrosis. If then, the existence of any influx of tracer into the area of infarction is accepted, the concentration of tracer will depend not simply on the rate of entry but on the relation between the rates of entry and exit. Changes in vascular permeability and changes in tissue binding of Hg^{203} are two possible factors which influence retention of the tracer. Nordenström's arteriographic demonstration of increase in collaterals around an area of previous myocardial infarction may also be significant in this regard.[9] The relationship between the uptake of Hg^{203} in myocardial infarcts and its uptake by certain brain tumors is at present unknown.

The fact that renal infarcts appear as "cold" areas with Hg^{203}-chlormerodrin, whereas myocardial infarcts are "hot," should cause no surprise, since the extremely high concentration of Hg^{203}-chlormerodrin by *normal* kidney makes it a special case. A somewhat analogous situation has long been known to exist with regard to I^{131} uptake by thyroid cancer, which usually appears as a "cold" area in comparison with the normal thyroid gland, but often appears "hot" after all normal thyroid tissue has been removed

Table II. Relative concentration of Hg^{203} in heart*

Dog number	Status	Posterior left ventricle (normal)	Anterior left ventricle (normal)	Anterior left ventricle (ligated)†	Difference between anterior and posterior left ventricle	Atrium
1.	Ligated	0 15	—	0 87	0.72	0 26
2.	Ligated	0 23	—	2 93	2.70	0 30
6.	Ligated	0 26	—	1 61	1 35	0 24
7.	Ligated	0 32	—	1 04	0 72	0 39
8.	Ligated	0 48	—	2 46	1.98	0 65
9.	Ligated	0 31	—	1 31	1.00	0 44
10.	Ligated	0 45	—	0 99	0 54	2.88
12.	Ligated	0 91	—	2 01	1 10	1 04
13	Ligated	4 53	—	11 90	7 37	2.32
					Mean 1 94‡	
3.	Sham operation	—	0 28	—	—	0 29
4.	Sham operation	0 31	0 32	—	0.01	0 49
5.	Sham operation	0 26	0 30	—	0 04	0 18
11.	Sham operation	0 56	0 59	—	0 03	0 86
14.	Sham operation	1 27	1 30	—	0 03	1.94
					Mean 0 03§	

*Relative concentration = $\frac{\frac{\Sigma x}{n}}{B}$, where $x = [Hg^{203}]$ in a single sample, n = number of samples of a given dog's tissue, and $B = [Hg^{203}]$ in blood

†As explained in the text, this comprises both infarcts and "ischemic" areas

‡This difference is significantly greater than zero ($p < 0.025$)

§This difference is not significantly greater than zero.

coronary ligation. The technique of projection of cardiac outlines and the results of excised heart scans and tissue counting indicate that the "hot" areas in the scans made in vivo did not come from noncardiac areas, e.g., the fundus of the stomach or the incision used in creating the infarct. Moreover, the incision was made in the lateral thoracic wall in such a way that any concentration of Hg^{203} in the incision would not be confused with the concentration in infarct in any event.

Among thoracic organs, rib, fat, and muscle did not have sufficient uptake of Hg^{203} to interfere significantly with the cardiac scans. In spite of the high concentration of Hg^{203} *per unit weight* of lung tissue, the lungs were not visualized in the photoscintigrams, because most of the volume of the intact lung is air. A more surprising result was our failure to visualize clearly the 21-day-old infarct, despite the *high concentration of Hg^{203} in the* lesion; the wall in the area of the infarct was, of course, thinner than uninvolved wall but was still about two thirds of normal thickness.

The high absolute concentrations of Hg^{203} in blood at the early intervals after injection did not per se prevent satisfactory scans, since the concentration of Hg^{203} in abnormal tissue was also very high at these early intervals; visualization of abnormal tissue depends inter alia upon the *ratio* of concentration of Hg^{203} in the tissue to the concentration in blood. *But there* was a definite trend toward higher *relative* concentrations of Hg^{203} at later times after injections of the tracer, i.e., the concentration of Hg^{203} in blood fell more rapidly than that in tissue. *This suggests* that scans made at 8 or 24 hours should show relatively less background radioactivity in blood than scans made during the first 8 hours after injection. As noted previously, this *may* have practical importance in

Comparison of the colloidal chromic phosphate and BSP clearance methods for estimating hepatic blood flow

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Hepatic blood flow in man is usually estimated by the clearance method first described by Bradley and associates[1] in 1945. This technique requires hepatic venous catheterization and sampling because the clearance of Bromsulphalein (BSP) or other dyes[2,3] is incomplete and varies with the functional state of the liver. The availability of a substance extracted solely and completely by the hepatic-portal bed in a single circulation, independent of hepatocellular function, would make it possible to estimate hepatic blood flow by peripheral blood concentrations alone.

After studying the behavior of colloidal materials injected intravenously, Dobson,[4] in 1952, recommended using the peripheral disappearance rate of colloidal chromic phosphate labeled with radiophosphorus as a measure of hepatic blood flow. He found that the colloid was almost completely removed in a single circulation by the reticuloendothelial cells, with deposition of from 85 to 90 per cent of the injected dose in the livers and spleens of mice, dogs, and rabbits. When the P^{32} activity of serial samples of blood was plotted on a logarithmic scale as a function of time, a curve was obtained in which the first 5 to 10-minute period described a straight-line downslope.[5] This early downslope approximated a simple exponential function represented by the equation

$$C_t = C_o e^{-kt},$$

in which C is the concentration at any time t, C_o is the initial concentration, and k is a constant. If complete extraction is assumed, the slope of this line would represent the fraction of the blood volume perfusing the liver per unit time. This slope, termed the *disappearance rate constant*, is identical to k in the equation and can be calculated from the half-time of disappearance of the P^{32} by the expression

$$k = \frac{0.693}{t^{1/2}}.$$

Calculation of the hepatic blood flow in man from the colloid disappearance rate has been reported to provide values which agree closely with those obtained by other investigators using the BSP method of Bradley.[5,6] Such correlation, however, between averages of different series may be fortuitous. The purpose of

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and the cancer is then being compared with other, normal neck tissues which have very low uptakes of iodine.*

The high concentration of Hg^{203} in areas of "ischemia" without frank necrosis is a finding of particular interest. Since postmortem examinations showed that the coronary ligature had held in every dog, it appeared reasonable to classify tissue distal to the ligature as abnormal in every instance, even in the absence of demonstrable infarction. The finding of a high concentration of Hg^{203} in 15 of 16 such noninfarcted samples distal to ligation is further validation that the areas were indeed abnormal, and even suggests that in certain dogs the tracer studies were a more sensitive index of damage than histologic findings.

Possible clinical applicability. Photoscanning after administration of Hg^{203}-chlormerodrin is now under study for the diagnosis of human myocardial infarctions. There is no a priori reason why the technique developed in dogs should not be applicable to man. However, the highest dose of Hg^{203} in common clinical use now is 700 μc (for the visualization of brain tumors). If one wishes to use a dose no higher than this for the visualization of myocardial infarcts in man, then the *relative* dose (microcuries per kilogram) in man will, of course, be considerably lower than that employed in dogs in the present study. It is possible, therefore, that the diagnosis of myocardial infarction in man after 700 μc of Hg^{203}-chlormerodrin may have to await improvement in the sensitivity of our instruments. Because photoscanners have been available for only a short period of time, expectation of such improvement does not seem visionary.

If successful, the usefulness of such a technique in clinical medicine would presumably be very high. Four possible special uses might be: diagnosis in patients with doubtful history or electrocardiogram (including patients with severe ischemia but no infarct); accurate localization of infarcts by direct visualization; direct demonstration of the progress of extension of an infarct; and recognition of impending infarction through localization of the tracer in areas of severe ischemia. Two important points of safety have already been established: the high specific activity of Hg^{203}-chlormerodrin preparations already commercially available allows one to limit the dose of stable mercury to negligible amounts; and the mechanical arrangement of the scanner makes it entirely feasible to scan a patient without moving him from his bed. Therefore, although the transition from dog to man will not necessarily be either simple or immediate, we are encouraged to report that a technique of diagnosis of myocardial infarction in dogs by photoscanning is now available, and that the method suggests, at least in principle, considerable usefulness and safety if it can be adapted to man.

*This analogy is, of course, only partly valid, since changes in secretion of TSH after thyroidectomy may affect the uptake by thyroid cancer.

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Table I. Comparison between the BSP and P^{32}-colloidal chromic phosphate methods for estimating hepatic blood flow

Subject	EHBF (BSP) (ml./min.)	EHBF (P^{32}) (ml./min.)	Deviation* (per cent)	EHBF (P^{32}) corrected† (ml./min.)	Deviation‡ (per cent)
Preparation A:					
W.R. (control)	1,100	941	−14	1,400	+27
W.R. (guanethidine)	700	569	−19	849	+21
O.T. (control)	1,500	714	−52	1,585	+ 6
O.T. (guanethidine)	900	541	−40	872	− 3
J.F. (control)	2,100	1,023	−51	2,130	+ 1
J.F. (guanethidine)	2,400	1,219	−49	2,257	− 6
J.D. (control)	2,400	950	−60	2,370	− 1
J.D. (guanethidine)	1,890	950	−50	1,900	0
Preparation B:					
J.P. (control)	1,337	1,485	+11	1,950	+47
J.P. (guanethidine)	910	913	0	1,350	+44
R.R. (control)	675	887	+31	1,085	+59
R.R. (guanethidine)	525	837	+60	985	+87
H.J.	1,600	1,135	−29	1,570	− 2
J.J.	1,800	1,838	+ 2	2,387	+32

$*\frac{EHBF(P^{32}) - EHBF(BSP)}{EHBF(BSP)}$ $\dagger\frac{EHBF(P^{32})}{\text{extraction ratio}}$ $\ddagger\frac{\frac{EHBF(P^{32})}{E.R.} - EHBF(BSP)}{EHBF(BSP)}$

blood flow derived from the peripheral disappearance rate in this group were corrected for incomplete extraction by dividing by the average extraction ratio for that particular colloidal injection, the values approximated the BSP results much more closely (Table I), the average deviation between the two methods was 8 per cent.

Preparation B was used in the 6 determinations carried out in the other 4 patients. In this group the peripheral disappearance rate of P^{32} provided higher estimates of hepatic blood flow than did BSP in 4 of the 6 simultaneous determinations (Table I). The extraction ratios of the colloid (mean 77 per cent) were significantly greater than those found with Preparation A (Table II). When these values were corrected for incomplete extraction, the resulting estimations of hepatic blood flow averaged 44 per cent higher than those with BSP.

Changes in hepatic blood flow after the administration of guanethidine were studied in 6 patients. Changes in blood flow indicated by clearance of BSP were reflected accurately by changes in the disappearance rate of P^{32} when the values were corrected for incomplete extraction. When the extraction ratio was not used, however, a change in blood flow in 1 patient was not detected, and a fairly wide divergence from the BSP value was noted in 2 others (Table III).

Discussion

If the colloid disappearance rate is to be used to estimate hepatic blood flow in normal man, the material must be cleared completely by the liver and spleen in a single circulation, and extrasplanchnic removal must be negligible. In order to use the method to study the effects of disease or drugs on blood flow in the liver, it must further be demonstrated that the efficiency of extraction of the colloid is not altered in these situations.

The low extraction ratios noted in this study indicate that clearance of the colloid in a single circulation is not complete even in patients without liver disease. That the

this study was to evaluate further the colloidal chromic phosphate method by comparing the values for estimated hepatic blood flow derived from the peripheral disappearance rate of the radioactive colloid with simultaneous clearance values obtained with the BSP method, and by determining the accuracy of the method in following drug-induced changes in blood flow.

Method

The studies were performed on 8 hypertensive patients. All subjects were free of clinical or laboratory evidence of liver disease except 2 (J. F. and H. J.), who gave histories of heavy alcoholic ingestion and had slightly elevated retention of BSP. A constant infusion rate of BSP was maintained by use of a Harvard infusion pump. The right hepatic vein was catheterized from the right antecubital approach. The brachial artery was cannulated percutaneously for the sampling of blood. Samples of arterial and hepatic venous blood were collected at 10-minute intervals, and hepatic blood flow was estimated from the clearance of BSP for at least three control periods.[1] Colloidal chromic phosphate was injected during the final control period. Two commercially available preparations of the colloid were used.* Five-tenths to 1 ml. of the colloid containing 5 to 10 microcuries of P^{32} was preloaded in a polyethylene catheter which had been threaded through a left antecubital vein into the subclavian vein. The chromic phosphate was flushed in with a rapid injection of 10 ml. of saline, and samples of blood were collected in heparinized tubes at 2-minute intervals for 10 minutes. The plasma was separated, planchetted, dried, and analyzed for beta activity, using a Nuclear-Chicago Model E 115 automatic low-background system with a Nuclear-Chicago Model 181A decade scaler. Plasma volume was measured with T-1824 dye.

On semilogarithmic paper, beta activity of the plasma samples was plotted on the ordinate and time on the abscissa. A straight line was fitted to the observed values, and the slope of this line, k, was calculated from the $t^{1/2}$ time in minutes (Fig. 1). The hepatic blood flow, in milliliters per minute, was obtained by multiplying k by the blood volume in milliliters. These values for hepatic blood flow were compared to the values obtained by averaging the control measurements of clearance of BSP for each patient.

Determinations in 6 patients were repeated after a steady state had been reached after the intravenous administration of guanethidine (0.75 mg. per kilogram). The average estimation of hepatic blood flow for several periods of clearance of BSP was again compared to the results of disappearance of colloidal chromic phosphate during the final period.

Results

The results obtained in 14 simultaneous determinations of hepatic blood flow by the BSP and P^{32}-chromic phosphate methods are compared in Table I. Only two of the values obtained using the P^{32} peripheral disappearance rate fell within 10 per cent of the simultaneous BSP result. The 8 determinations in the first 4 patients were carried out using Preparation A. In this group the P^{32} results were consistently lower (average 42 per cent) than the estimations using BSP. The hepatic extraction ratios of the colloid (Table II) averaged only 54 per cent (range 40 to 67 per cent). When the values for hepatic

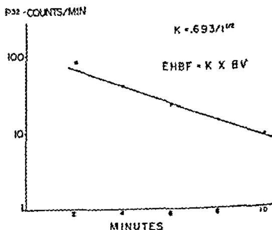


Fig. 1. Plot of peripheral disappearance rate of colloidal chromic phosphate labeled with P^{32} in Subject J. F. (guanethidine); $t^{1/2}$ 2.9 minutes, k value .238, blood volume 5,122 ml.

*Preparation A was obtained from Volk-Radio-Chemical Co., Chicago, Ill., and Preparation B was obtained from Abbott Laboratories, North Chicago, Ill.

comparing results for hepatic blood flow calculated by this method with simultaneous measurements using the BSP clearance method.

One commercial preparation of colloid was extracted by the liver with an efficiency which averaged 54 per cent. The other preparation was extracted with an average of 77 per cent efficiency but also was removed significantly by extrasplanchnic cells. The incomplete and variable extraction of the colloid by the liver, the appearance of significant extrasplanchnic extraction when particle size favors efficient removal, and the effect of hepatic disease and/or changes in hepatic blood flow on extrasplanchnic phagocytosis all contribute to the possibilities of error when this method is applied in man.

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Table II. Extraction ratios of P^{32}-labeled colloidal chromic phosphate

Patient	*Test period*	*Extraction ratio**
Preparation A:		
W.R.	Control	.67
	Guanethidine	.67
O.T.	Control	.45
	Guanethidine	.62
J.F.	Control	.48
	Guanethidine	.54
J.D.	Control	.40
	Guanethidine	.51
Average		.54
Preparation B:		
J.P.	Control	.70
	Guanethidine	.76
R.R.	Control	.82
	Guanethidine	.85
H.J.	Control	.72
J.J.	Control	.77
Average		.77

$$\text{*Extraction ratio} = \frac{\text{Counts (arterial-hepatic vein)}}{\text{Arterial counts}}$$

Table III. Percentage changes in EHBF after guanethidine, using the P^{32} and BSP methods simultaneously

Subject	*Change in EHBF after guanethidine*		
	(P^{32}) (per cent)	*(P^{32})/Extraction ratio (per cent)*	*(BSP) (per cent)*
W.R.	−39	−39	−36
O.T.	−23	−44	−40
J.F.	+16	+ 4	+14
J.D.	0	−21	−21
J.P.	−38	−33	−32
R.R.	− 5	− 9	−22

incomplete extraction may be due at least in part to the characteristics of the injected colloidal particles may be inferred from the differences in behavior between the two preparations used. It would appear from our data that Preparation A contained a larger proportion of small particles or of free P^{32}, thus impairing its removal by phagocytic cells.

Dobson[4] noted species differences in localization of injected colloid; some animals accumulated up to 15 per cent of the material in the bone marrow and other reticuloendothelial cells outside of the liver and spleen. Significant extrasplanchnic removal of the colloid would provide falsely high values for hepatic blood flow. Preparation A, with its relatively low hepatic extraction, apparently was not removed to an appreciable degree outside of the splanchnic bed, since correction for incomplete hepatic extraction gave results which approximated the BSP values. Preparation B was extracted more completely by the liver and probably also was removed by extrasplanchnic cells, as evidenced by the considerably higher values for hepatic blood flow than were obtained by the BSP method.

The effect of hepatocellular disease on the phagocytic activity of the liver is not clearly established. Recent studies have demonstrated that the peripheral disappearance rate of colloidal chromic phosphate is not reduced significantly in patients with severe liver disease.[7,8] Rankin and associates,[9] however, have presented evidence that hepatic extraction efficiency decreases in patients with liver disease, and that the disappearance of the colloid from the circulation in these patients is due to more prominent bone marrow phagocytosis. The same phenomenon of more active extrasplanchnic extraction with lower hepatic blood flows was suggested in our studies using colloid Preparation B. Corrected disappearance rates in these subjects gave the greatest overestimations of hepatic blood flows when the hepatic blood flows were lowest (Table I). It would appear from these studies that none of the criteria necessary to validate use of the peripheral disappearance rate of commercial colloidal chromic phosphate to measure hepatic blood flow in man are consistently fulfilled.

Summary and conclusions

The simplified method of estimating hepatic blood flow in man by measuring the peripheral disappearance rate of P^{32}-labeled colloidal chromic phosphate was evaluated by determining the hepatic extraction ratios of the colloid and by

a given pair of isophasic points K and L. Given a point in loop K, the isophasic point in loop L can be pointed out with sufficient accuracy if one considers characteristic irregularities present in both loops and makes use of time-markings. Thus, one gets three equations with nine unknowns. In order to obtain the unknowns from the equations, six other equations are necessary, which can be acquired by measuring the coordinates of a second and a third pair of points K and L. In this manner the complete set of transformation equations is secured for one individual from three measured pairs of points.

If this transformation were found to satisfy other random pairs of points K and L in the same individual, this would only make plausible in a single individual the basic assumption concerning the stationary dipole. As to the validity of this "*individual transformation*" for other individuals, it would hardly be likely that a transformation calculated for one individual would best fit any other individual. It is necessary, therefore, to study a sufficiently large number of cases and to calculate an "*average transformation*," i.e., that transformation which gives, on the average, for each individual case the best possible result. Such transformation formulas could be made available for every existing combination of two systems of VCG. In this way it would be possible to bring about an optimal approximation of any one system to another, while maintaining the characteristic electrode positioning of each system. Complete identity of two systems appears if, in formula (1), the transformation coefficients on the diagonal $p_x = q_y = r_z = 1$, while the other coefficients all are equal to zero. Thus, the mathematical transformation may give an impression of the extent and manner of deviation or agreement between two systems. Moreover, an accurate mathematical formulation of the extent of this agreement can be derived, using the nine coefficients. The results of such an exact mathematical treatment will be compared with the subjective evaluation on the basis of clinical criteria.

Material and instrumentation

The four systems that we have investigated have in common the fact that they are all based on a rational physical foundation. These are the systems proposed by Burger and associates[2] (B_1W_4''), Schmitt and Simonson[4] (SVEC-III), Frank[5] and McFee and Parungao,[6] which will be referred to by the letters B, S, F, and M, respectively.

McFee's system was not yet published at the time this investigation was made We received the pertinent data through personal communication After our data were collected and elaborated, we received word that the author had made several alterations in his system. As far as numerical changes were concerned, these were easily accounted for in the calculations. There were also alterations made in electrode arrangement, but these could not be considered in this study, because the clinical measurements had already been made We placed the triangular set of precordial electrodes in such a way as to enclose the heart, instead of placing the triangle with its geometrical center above the heart's center of gravity. In practice this hardly leads to an appreciable difference in positioning The electrodes on the left side were placed 2 5 cm cranially and caudally to the level of the geometrical center of the precordial triangle, instead of 5 cm as is now recommended Experience has since shown that these changes have but little effect on the configuration of the vectorcardiogram

The axial directions are those commonly used in vectorcardiography. X = right−, left+; Y = cranial−, caudal+, Z = ventral−, dorsal+.

The vectorcardiograph was constructed in our laboratory.[7] The instrument has four channels, making it possible to take up four leads without using an external network. The F-system would require the use of five channels if the projections were recorded one after another, and six channels if recorded simultaneously. In this system, therefore, an external network was necessary; the network was kept as simple as possible by accepting the limitation of successive recording of the projections. In the case of the other systems, however, horizontal and frontal projections were simultaneously photographed from two cathode-ray tubes. Thus, to the deflection plates of the oscilloscopes are simultaneously applied the X (two times), Y and Z components of the vector. Each component can be composed as a linear function of four contributing voltages—one per channel—since each channel possesses four outputs—one for each component (X two times). The output voltages can be regulated with potentiometers and sign switches, thus allowing the setup of the appropriate lead-coefficients for each vector component. To this purpose, four separate panels, each containing sixteen potentiometers with their sign switches, have been added to the instru-

Compromise in vectorcardiography
II. Alterations of coefficients as a means of adapting one lead system to another

Subjective and mathematical comparison of four systems of VCG

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In our previous article,[2] we stated that one VCG system (specifically SVEC-II) can be more or less adapted to another (specifically B_1W_1'') by means of an appropriate change in the positioning of the electrodes. The extent to which it was possible to make the former system conform to the latter, however, was not satisfying. Therefore, we decided to revert to the second method in which such an adaptation can be realized, viz., that of altering the set of coefficients whereby the leads are multiplied in the linear functions giving the components of the heart vector.

If two VCG systems K and L are completely identical, the coordinates of any two randomly chosen corresponding points in loop K and loop L will be identical:

$$X_K = X_L,\ Y_K = Y_L,\ Z_K = Z_L.$$

We understand "corresponding points" to be isophasic, i.e., they are temporally coincidental in the cardiac cycle. In case the systems in question differ, one can attempt to determine by which function the coordinates of a general point of L can be transformed into the coordinates of its isophasic point in K. In an earlier publication,[3] we applied a graphic approach to this determination: at present we shall give a numerical treatment to the problem. Assuming that the electrical action of the heart can be described as that of a stationary dipole, one can prove that a transformation, as mentioned above, can be represented by such a system of linear equations, that each coordinate of a general point K becomes expressed in all the coordinates of an isophasic point L:

$$\begin{aligned} X_K &= p_x X_L + q_x Y_L + r_x Z_L \\ Y_K &= p_y X_L + q_y Y_L + r_y Z_L \\ Z_K &= p_z X_L + q_z Y_L + r_z Z_L \end{aligned} \qquad (1)$$

In this system there are nine coefficients p_x . . . . . . r_z, which are dimensionless quantities that are dependent on the directions of the coordinate axes. These are not vector, but tensor components. They are the unknowns in formula (1). The values X_K, Y_K, Z_K, and X_L, Y_L, Z_L are knowns, because they can be determined by measuring the coordinates of

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and are valid for the transformation L→K. The standard errors in $p_{x(L\to K)}$ · · · · · · · · $r_{z(L\to K)}$ can also be calculated.

Transformations and standard errors were in this way determined for four independent relations between the four VCG systems under investigation, viz., B→M, B→F, M→F, and M→S, and their reverses.

The reader is referred to the usual textbooks for a treatment of the method of least squares and of the calculation of standard errors in this method. It must be pointed out here, however, that it is incorrect to use a primarily found relation, e.g., B→M, to calculate its reverse, M→B. This may be shown for the one-dimensional case (points on the X axis): if a number of points X_K and X_L be given and the general point X_L is to be transformed to X_K by means of the formula $X_{(L\to K)} = p_{(L\to K)} X_L$, then p is found, using least squares, from the equation:

$$\Sigma X_K X_L = p_{(L\to K)} \Sigma X_L^2$$

The reverse transformation $X_{K\to L} = p_{(K\to L)} X_K$ gives the equation:

$$\Sigma X_L X_K = p_{(K\to L)} \Sigma X_K^2$$

It is seen that $p_{(L\to K)} \neq \dfrac{1}{p_{(K\to L)}}$. For analogous reasons it is not permitted to calculate two relations, e.g., B→M and B→F, and then derive the third, M→F, secondarily from these. Therefore, any transformation between any two systems must be calculated independently and directly from the measured values of the coordinates of the points, using a set of formulas of the type of formula (2).

In the course of the investigation it became apparent that S was in very good agreement with M and F (see page 675). For this reason and because it is technically the more complicated system, we felt justified in discarding it in the future. To cut down on the already large amount of arithmetical labor, we also decided to omit the calculation of the B⇆S and F⇆S transformations.

As stated in the introduction, it is now possible with the aid of the transformations obtained to quantitatively formulate the degree to which two VCG systems K and L differ. Since a transformation is constructed to bridge the difference between two systems, the transformation is in itself a measure of this difference. The transformation, in turn, is measured by the change it effects on the system to which it is applied. So, when system L is transformed toward system K, resulting in a system L→K, the extent of the change in system L is given by the average displacement undergone by the points of L, i.e., the average distance L−L→K of a point of L to its isophasic point on L→K. This distance is expressed in the changes of the coordinates by the well-known formula:

$$(L - L\to K)^2 = (X_{L\to K} - X_L)^2 + (Y_{L\to K} - Y_L)^2 + (Z_{L\to K} - Z_L)^2 \quad (4)$$

With the help of formula (3) the changes of the coordinates may be written in the following form:

$$\begin{aligned} (X_{L\to K} - X_L) &= (p_{x(L\to K)} - 1)X_L + q_{x(L\to K)} Y_L + r_{x(L\to K)} Z_L \\ (Y_{L\to K} - Y_L) &= p_{y(L\to K)} X_L + (q_{y(L\to K)} - 1) Y_L + r_{y(L\to K)} Z_L \\ (Z_{L\to K} - Z_L) &= p_{z(L\to K)} X_L + q_{z(L\to K)} Y_L + (r_{z(L\to K)} - 1) Z_L \end{aligned} \quad (5)$$

Substitution of formula (5) in formula (4) gives:

$$\begin{aligned} (L - L\to K)^2 = \\ &= \{ (p_{x(L\to K)} - 1)^2 + p_{y(L\to K)}^2 + p_{z(L\to K)}^2 \} X_L^2 + \\ &+ \{ q_{x(L\to K)}^2 + (q_{y(L\to K)} - 1)^2 + q_{z(L\to K)}^2 \} Y_L^2 + \\ &+ \{ r_{x(L\to K)}^2 + r_{y(L\to K)}^2 + (r_{z(L\to K)} - 1)^2 \} Z_L^2 + \\ &+ 2 \{ q_{x(L\to K)} (p_{x(L\to K)} - 1) + p_{y(L\to K)} (q_{y(L\to K)} - 1) + p_{z(L\to K)} q_{z(L\to K)} \} X_L Y_L \\ &+ 2 \{ r_{x(L\to K)} (p_{x(L\to K)} - 1) + p_{y(L\to K)} r_{y(L\to K)} + p_{z(L\to K)} (r_{z(L\to K)} - 1) \} X_L Z_L \\ &+ 2 \{ q_{x(L\to K)} r_{x(L\to K)} + r_{y(L\to K)} (q_{y(L\to K)} - 1) + q_{z(L\to K)} (r_{z(L\to K)} - 1) \} Y_L Z_L \end{aligned} \quad (6)$$

The displacement is equal to zero if $p_{x(L\to K)} = q_{y(L\to K)} = r_{z(L\to K)} = 1$, while all the other coefficients are equal to zero. It is obvious from formula (5) that then:

$$X_{L\to K} = X_L,\ Y_{L\to K} = Y_L,\ Z_{L\to K} = Z_L$$

The transformation in this case is called the identical one. Since the aim is to find a measure

ment. On each panel the potentiometers can be preset to the coefficients of a different system. The four different panels can be connected consecutively by means of a selector switch; this avoids time-consuming adjustment of the potentiometers between the recordings of the individual systems. The placement of the electrodes of all four systems on the patient's body is also made beforehand, in so far as possible. By means of these arrangements it is possible to reduce to about 20 minutes the time necessary for examining one patient with four systems.

A total of 169 persons was examined: 41 normal subjects (9 children under the age of 12 years) and 128 patients with heart disease (33 under the age of 12 years).

Method

As said above, to calculate the transformation in one individual, for each component of the heart vector three equations of the type:

$$X_K = p_x X_L + q_x Y_L + r_x Z_L \tag{1a}$$

are required, necessitating three pairs of points K and L. If more than three equations are supplied (by measuring more than three pairs of points), the unknowns become overdetermined. To solve the equations in such a case, use can be made of the method of least squares. There is, indeed, no objection against increasing the number of equations. In our case, instead of determining a transformation per individual and calculating an average transformation therefrom, we preferred to pool the equations pertaining to each component of the vector, from all subjects. Then, a single calculation was carried out to find the desired "average transformation," employing the above-mentioned method of least squares. Moreover, the number of pairs of isophasic points per individual was not limited to three but five were measured, since by using a greater number of points the loops become better defined and the total number of equations is increased. In this manner the average transformation can be calculated with greater accuracy. Thus, for each vector component 845 equations (169, the number of subjects, × 5) were procured, from which the coefficients p, q, and r had to be solved as unknowns—a total, therefore, of 2,535 equations for all three of the vector components. For these calculations a simple electric calculator was utilized.

The points were all taken from the QRS complex, since it is difficult to identify isophasic points on the P or T loops. Therefore, one could object that the transformations obtained are not valid for the P or T loops. In order to check this, transformations were calculated using a limited number of points obtained from the T complex. These transformations fitted in satisfactorily with those previously calculated for the QRS complex.

The method of least squares supplies the following so-called normal equations for the transformation coefficients of formula (1a):

$$\begin{aligned} \Sigma X_K X_L &= p_x \Sigma X_L^2 + q_x \Sigma X_L Y_L + r_x \Sigma X_L Z_L \\ \Sigma X_K Y_L &= p_x \Sigma Y_L X_L + q_x \Sigma Y_L^2 + r_x \Sigma Y_L Z_L \\ \Sigma X_K Z_L &= p_x \Sigma Z_L X_L + q_x \Sigma Z_L Y_L + r_x \Sigma Z_L^2 \end{aligned} \tag{2}$$

Herein the Σ signs signify the sums of the values of $X_K X_L$, X_L^2, $X_L Y_L$, etc., from all 845 equations. Similar normal equations can be formulated for the transformation coefficients p_y, q_y, r_y, and p_z, q_z, r_z of the Y and the Z components of the heart vector. From these three sets of equations the values of p_x, q_x, r_x, p_y, q_y, r_y, and p_z, q_z, r_z can be calculated and substituted in formula (1). At this point the average transformation of system L into system K is known. As it were, a new VCG system L→K is gained, identical to L with regard to electrode positioning, but having, on the average, the configuration of K. For this system, formula (1) is written in the form:

$$\begin{aligned} X_{L\to K} &= p_{x(L\to K)} X_L + q_{x(L\to K)} Y_L + r_{x(L\to K)} Z_L \\ Y_{L\to K} &= p_{y(L\to K)} X_L + q_{y(L\to K)} Y_L + r_{y(L\to K)} Z_L \\ Z_{L\to K} &= p_{z(L\to K)} X_L + q_{z(L\to K)} Y_L + r_{z(L\to K)} Z_L \end{aligned} \tag{3}$$

The notation $p_{x(L\to K)}$ . . . . . $r_{z(L\to K)}$ indicates that these coefficients are now knowns.

$$\sigma^2 = (X_K - X_{L\to K})^2 + (Y_K - Y_{L\to K})^2 + (Z_K - Z_{L\to K})^2$$

If the coordinates of L→K are again expressed in those of L, according to formula (3), the result is:

$$\sigma = \sqrt{\{ (p_{x(L\to K)}X_L + q_{x(L\to K)}Y_L + r_{x(L\to K)}Z_L - X_K)^2 + (p_{y(L\to K)}X_L + q_{y(L\to K)}Y_L + r_{y(L\to K)}Z_L - Y_K)^2 + (p_{z(L\to K)}X_L + q_{z(L\to K)}Y_L + r_{z(L\to K)}Z_L - Z_K)^2 \}}$$

The second member is computed by substituting for X_L^2, X_LY_L, etc., the values of $\Sigma X_L^2/n$, $\Sigma X_LY_L/n$, etc., as previously done. In order to obtain again a relative measure, σ is divided by the average size of the loops; the resulting quantity is called Δ:

$$\Delta = \frac{\sigma}{\sqrt{\left(\frac{\Sigma X^2}{n} + \frac{\Sigma Y^2}{n} + \frac{\Sigma Z^2}{n}\right)}}$$

The agreement between systems was evaluated by subjective judgment as well. The method, used routinely by us,[2,3,9,10] and also applied in various forms by others,[11,12] consists of independent evaluation by three observers who express the agreement between any two systems by means of a rating for the horizontal and also for the frontal projections, using a scale of 0 to 10. (We are aware that in this manner the X component enters twice into the evaluation.) For every comparison of two systems the average rating was determined from the total number of cases. Thus, for the four systems, six average ratings with their standard errors were found.

Finally, the validity of the obtained transformation can be tested in practice. To this end the VCGs recorded by using the new system L→K should be compared with those recorded by system K. In making L→K vectorcardiograms, the electrode positioning of system L is maintained. Each vector component of L→K is obtained as a linear function of the three vector components of L by using the appropriate transformation coefficient for each L component. Since each L component is constructed as a linear function of several leads, every single lead, in turn, must be multiplied by this same transformation coefficient. The values which in this way are determined for the leads composing each vector component of L→K can be set up on one of the panels of the vectorcardiograph by means of the potentiometers (see page 667). On two other panels the systems K and L can be set up. Thus in one patient the systems K, L, and L→K can be rapidly taken up successively, to be compared afterward. The agreement between the systems is again subjectively evaluated. Improvement in the agreement as a result of the transformation will show itself in a higher rating for the comparison of L→K with K, than for that of the original L with K.

Results and discussion

Initially, separate transformation formulas were calculated for various nosological entities, e.g., right ventricular hypertrophy due to pulmonary stenosis, atrial septal defect, etc., as well as for the normal group. Since no differences became apparent the groups were combined.

With the help of the equations derived from the measured points, the following transformation formulas were calculated, together with the standard errors of the coefficients:

B→M
$$X_{B\to M} = +(0.71 \pm 0.013)X_B + (0.22 \pm 0.028)Y_B + (0.24 \pm 0.019)Z_B$$
$$Y_{B\to M} = +(0.05 \pm 0.007)X_B + (0.97 \pm 0.011)Y_B - (0.17 \pm 0.010)Z_B$$
$$Z_{B\to M} = -(0.39 \pm 0.021)X_B + (0.60 \pm 0.033)Y_B + (0.92 \pm 0.030)Z_B$$

B→F
$$X_{B\to F} = +(0.69 \pm 0.017)X_B + (0.33 \pm 0.026)Y_B + (0.14 \pm 0.024)Z_B$$
$$Y_{B\to F} = +(0.06 \pm 0.010)X_B + (1.05 \pm 0.016)Y_B - (0.05 \pm 0.015)Z_B$$
$$Z_{B\to F} = -(0.22 \pm 0.020)X_B + (0.36 \pm 0.031)Y_B + (0.70 \pm 0.028)Z_B$$

M→F
$$X_{M\to F} = +(0.94 \pm 0.012)X_M + (0.14 \pm 0.016)Y_M - (0.07 \pm 0.012)Z_M$$
$$Y_{M\to F} = +(0.08 \pm 0.009)X_M + (0.99 \pm 0.011)Y_M + (0.08 \pm 0.009)Z_M$$
$$Z_{M\to F} = +(0.08 \pm 0.013)X_M - (0.07 \pm 0.017)Y_M + (0.72 \pm 0.013)Z_M$$

for the *average* displacement resulting from the L→K transformation, the *average* values of X_L^2, Y_L^2, etc., from all measured points (expressed by $\Sigma X_L^2/n$, $\Sigma Y_L^2/n$, *etc.*) must be substituted in formula (6). At this point, one could object to the fact that no scale for the different systems has been given; only in system B is it stated how one can obtain the heart vector in absolute measure (volt cm.²).[8] If two systems should happen to differ greatly in their sizes, then (L − L→K) would become large, without implying that a large essential difference was present. Therefore, it is necessary to begin by adjusting the scales of the different systems as accurately as possible. To this purpose the average size of the loops of a system was characterized by the quantity

$$\sqrt{\frac{\Sigma X^2}{n} + \frac{\Sigma Y^2}{n} + \frac{\Sigma Z^2}{n}}$$

Taking system B as the standard of reference (because in the case of B, absolute values are given), we adjusted the sizes of the other systems by means of a correction factor for each. Furthermore, since relative measures are more pertinent than absolute ones, in place of the absolute length of (L − L→K), a *relative* measure ∂ is introduced by relating (L − L→K) to the corrected average size of the loops:

$$\partial = \frac{\sqrt{(L - L \rightarrow K)^2}}{\sqrt{\left(\frac{\Sigma X^2}{n} + \frac{\Sigma Y^2}{n} + \frac{\Sigma Z^2}{n}\right)}}$$

From a formally mathematical point of view, a slightly different approach can be chosen to evaluate the change effected by a given transformation. In this procedure the transformation is applied to a sphere, instead of to a vectorcardiogram, and the displacement undergone by the points on the surface of the sphere is studied. This method postulates that all directions are equivalent (isotropism), in contradistinction to the previous treatment, wherein the directional prevalence intrinsic to the vectorcardiogram biased the average values of X_L^2, X_LY_L, etc., in formula (6) (anisotropism). The equation for a random point on a sphere is:

$$X^2 + Y^2 + Z^2 = R^2 \tag{7}$$

If the points are distributed evenly on the sphere, the average values of X^2, Y^2, and Z^2 are equal, and, thus, in view of formula (7), it is true that:

$$X^2 = Y^2 = Z^2 = 1/3\ R^2 \tag{8}$$

For a given X the probability of a positive or a negative Y is identical. Therefore, XY will, on the average, be equal to zero. The same applies to XZ and YZ, hence:

$$XY = XZ = YZ = 0 \tag{9}$$

By substituting formulas (8) and (9) in formula (6) the average displacement (L—L→K) of a point on the surface of the sphere is found. Again, the more preferred *relative* measure is obtained by relating (L—L→K) to the size of the sphere. This new measure is called D:

$$\frac{(L - L \rightarrow K)^2}{R^2} = D^2 = 1/3\ \{(p_{x(L\rightarrow K)} - 1)^2 + (q_{y(L\rightarrow K)} - 1)^2 + (r_{z(L\rightarrow K)} - 1)^2 + p_{y(L\rightarrow K)}^2 + p_{z(L\rightarrow K)}^2 + q_{x(L\rightarrow K)}^2 + q_{z(L\rightarrow K)}^2 + r_{x(L\rightarrow K)}^2 + r_{y(L\rightarrow K)}^2\} \tag{10}$$

The absence of terms containing coordinates shows that D is a rotational invariant, as may be anticipated from the isotropism. D is also not subject to the directional preferences of the vectorcardiogram, as opposed to ∂, in which the preferential directions manifest themselves. For the identical transformation D = 0, just as ∂ = 0.

The transformation L→K is, by definition, the transformation that changes system L in such a way that, *on the average*, the loops of L adopt the configuration of those of system K. However, the individual results of the transformation will be scattered around the "target," the actual system K. As a measure for the scattering, the average distance, σ, from the points of L→K to their isophasic points in K is taken. The distance between a general pair of isophasic points can again be represented, as in formula (4), by the differences of their coordinates:

No. 187			B	B→M	M
B					
B→M			*		
M			5 8	9 9	
F			5 8	7 8	7 7

No. 155			B	B→M	M
B					
B→M			*		
M			4 6	8 8	
F			4 6	6 6	7 7

No. 175			B	B→M	M
B					
B→M			*		
M			7 8	8 10	
F			7 9	7 8	8 8

No. 209			B	B→M	M
B					
B→M			*		
M			6 5	7 7	
F			4 4	5 5	5 6

No. 181			B	B→M	M
B					
B→M			*		
M			8 6	6 8	
F			6 7	5 6	6 8

No. 231			B	B→M	M
B					
B→M			*		
M			5 8	4 8	
F			5 7	4 7	7 8

Fig. 3. Vectorcardiograms were obtained with the B, M, and F systems as well as with the system B-transformed-to-M, and ratings were assigned to the agreement between systems. From all the ratings obtained three groups were singled out: Group 1, with marked improvement of the agreement between B→M and M as compared to B and M (increase in rating by 5 or 6 points for horizontal and frontal projections combined); Group 2, with fair improvement (2 or 3 points); and Group 3, with negative result (in no case exceeding minus 1 or 2 points). Examples, randomly picked, from Group 1 are presented in the upper row, from Group 2 in the middle, and from Group 3 in the lower row. In the vertical columns beside the vectorcardiograms the pertinent ratings are entered. *No ratings have been assigned to the agreement between B and B→M, since this relation is unequivocally and uniquely determined by a mathematical equation.

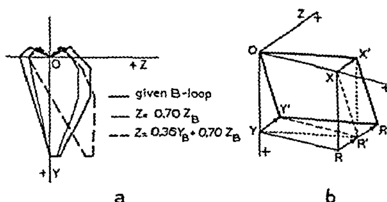


Fig. *1*. *a*, Illustrates the concept of shear. The B→F transformation for the *Z* component is applied to a schematized B loop which lies, in this case, in the *Y-Z* plane, so that at every point $X_B = 0$. The loop undergoes a shear in the *Z* direction, proportional to the distance along the *Y* axis. *b*, Illustrates an oblique shear. A shear in the *Z* direction, proportional to the distance in the *X* direction, applied to the plane *OYRX* produces the plane *OYR'X'*; if proportional to the distance in the *Y* direction, it produces the plane *OY'R'X*. An oblique shear is proportional to the distances along the *X* and *Y* axes, and results in the plane *OY'R''X'*.

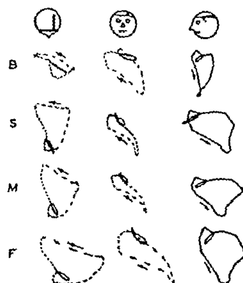


Fig. 2. Horizontal, frontal, and sagittal projections of the vectorcardiogram of a normal individual are shown, recorded according to systems B, S, M, and F. The sagittal projections were graphically constructed, utilizing the frontal and horizontal projections in the same system. The differences characteristic of the four systems are clearly shown.

$$\text{M}\rightarrow\text{S}\quad X_{M\rightarrow S} = +(0.86 \pm 0.010)X_M + (0.01 \pm 0.013)Y_M - (0.09 \pm 0.010)Z_M$$
$$Y_{M\rightarrow S} = +(0.01 \pm 0.005)X_M + (0.88 \pm 0.006)Y_M + (0.00 \pm 0.005)Z_M$$
$$Z_{M\rightarrow S} = +(0.21 \pm 0.016)X_M + (0.13 \pm 0.021)Y_M + (1.05 \pm 0.016)Z_M$$

The reverse relations have not been presented, since the above-written formulas convey a sufficient impression of the connections which exist between the various systems.

From the M→F transformation it appears that system F is smaller in sagittal magnitude than M; moreover, the Z component receives a small negative contribution in magnitude from the Y component of the transformed system. On the other hand, the Y component receives a positive contribution from the Z component. This shows itself in the case of a loop directed posterocaudally; such a loop in F is directed less posteriorly and more caudally than in M. A representative example is given in Fig. 2.

Since there is a good subjective agreement between M, F, and S, and since the M→F and M→S transformations point to a good measure of concordance between M and F and M and S, it may be inferred that the relation F⇄S will also be a close one. On the other hand, the relationship between B at one side and M, F (and S) as a group on the other shows some disparity. The transformations B→M and B→F present a strong analogy. The Y components again show very good agreement. In the transverse direction the systems M, F (and S) are narrower than B when in the vicinity of the X axis, but to the extent that a point is more distant from the origin in the Z or in the Y direction, the X components of these three systems receive a numerical contribution, proportional to Z_B and/or Y_B. The Z components receive a strong positive contribution from Y_B. This means that a caudally directed B loop, when transformed into M, F (or S), undergoes a marked shear, directed posteriorly. The negative contribution from X_B, moreover, causes the portion of the loop to the left of the origin to be displaced forwardly, and the portion to the right of the origin to be displaced to the rear (Fig. 2). This phenomenon is more marked for B→M than for B→F.

If the four systems are viewed globally, it can be said that M (and S) are directed more sharply dorsally, B caudally, whereas F tends to a mid-position, with a bias toward M and S.

The differences which exist between any two systems were, as described, expressed objectively in two ways: through means of ∂ (the anisotropic case previously defined; see page 669) and through means of D (the isotropic case; see page 670). The values found for ∂ and D are given in Table I, together with the ratings obtained by subjective evaluation of the agreement between any two systems (see page 671). As can be seen from the table, there is a reasonable correlation between these different methods of comparison. The good agreement between M, S, and F can also be observed. B stands apart to some extent. At this point it must be noted that the systems M, S, and F rest upon the same assumption, viz., the electrical homogeneity of the trunk, whereas in B an important degree of inhomogeneity is postulated.

∂ and D are relative measures of the average displacement, i.e., the displacement achieved by the *average* transformation. In addition, *individual* B→M transformations were calculated in a limited number of cases. Here, one can calculate in the same manner the displacement brought about by the transformation. Since such a transformation is tailor-made for each separate individual case, the displacement can assume much more extreme values. These values can vary between zero in the case of identical loops and very large magnitudes in the case of complete lack of agreement (see Table II). The average of the values of a large number of individual displacements should yield approximately the average ∂ or D calculated for the average transformation. From the foregoing it is apparent that an average transformation is, of necessity, a rather rough tool that is indiscriminately used, regardless of the requirements of the individual case; it is applied to cases in which agreement is already almost perfect, producing, in consequence, entirely negative results, as well as to cases with an almost complete absence of agreement, in which the results have to be deficient. Thus, it is impossible through means of an *average* transformation to achieve complete adaptation of one system to another, or, in other words, to reach an agreement which would be rated 10 or close to 10. The unavoidable scattering of the results of the transformation around the "target" prohibits such a performance. The extent of this scattering is calculated with the help of Δ, as described on page 670. The values of Δ for the four average transformations are also entered into Table I. It is seen from this table that the scatter is of the order of about 1.5 times the displacement, so that the effect of the transformation is not drowned in the scatter. It may be expected, therefore, that an average transformation will achieve an improvement in agreement. It is self-evident that

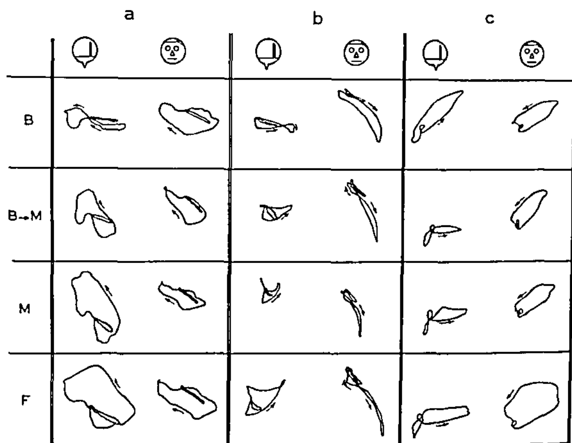


Fig. 4. Examples of successful application of the B→M transformation in three cases: *a*, An atrial septal defect of the secundum type, *b*, a case without definable abnormality ("functional" murmur), *c*, an atrial septal defect of the primum type.

On survey of these transformations, it is generally apparent that the Y components of any two systems which are being compared show good agreement, the X components show slightly less agreement, and the Z components show the least agreement of all. The discrepancy between the Z components of the various systems is a consequence of the uncertainty in determining the sagittal component of the heart vector, which is caused by the relatively small dimensions of the human thorax in the sagittal direction.

In the M and S systems the Y components are obtained in an identical manner, following the authors' instructions. The M→S transformation for the Y component must, therefore, be the identical one. The deviation from identity, appearing in the transformation equation, is a result of the preceding adjustment in scale which involves all three components and not only the component(s) causing the difference in size. In these two systems the X components also show *good agreement*. The Z component of S (in short: Z_S) is composed mainly of a numerical contribution proportional to Z_M; but also to be considered are contributions proportional to the magnitudes of X_M and Y_M. This implies that, for points close to the Z axis, Z_S is almost equal to Z_M, but that the points of loop M undergo a greater displacement in the Z direction as they become increasingly distant from the zero point in the X and Y directions. Such a displacement, which increases proportionally with the distance, is called a shear (Fig. 1,*a*). In the illustration it is assumed, for the sake of convenience, that the *X contribution is zero; in this case* a shear parallel to the Z axis is only produced proportional to the distance along the Y axis. In reality, there is also a shear proportional to the distance in the X direction, and, therefore, the loop as a whole is subject to an oblique shearing (Fig. 1,*b*). These shears are important in all transformations concerned.

Table II

Case number	∂	*D*	Δ
2.	0 54	1 02	0 17
7.	0 50	0.86	0.08
8.	0 91	3.10	0 17
10.	0 74	0 91	0 06
19.	0 35	0.36	0 05
23.	0.48	0.78	0 08
27.	0 27	0 59	0 06
28.	0 85	0.92	0.09
31.	0.93	1.40	0 13
33.	0 70	1.48	0.14

Individual B→M transformations were calculated in a limited number of cases, ten of which are presented here. The difference between the B and M loops in each case is again quantitatively expressed by ∂ and D. The accuracy of the individual transformations is shown by the Δs, which represent the residual differences after transformation between the target system and the transformed system. These differences are small (of the order of 10 or 20 per cent) in comparison to the differences, ∂ or D, respectively, prior to the transformation.

Table III

	Subjective rating	
	Frontal	*Horizontal*
Comparison:		
B→M and M	7 9 ± 0 10	6 7 ± 0.11
B and M	6 9 ± 0 10	5 8 ± 0 10
Improvement due to B→M transformation	1 0 ± 0 09	0 9 ± 0 10

The B→M transformation achieves a significant improvement in agreement between systems B and M according to subjective evaluation, using a scale of 0 to 10.

individual (or model) are applied to more individuals. The appearance of higher poles based on individual differences in body build cannot, in principle, be obviated, given the systems used in this study. This interindividual scatter is, however, of the same order of magnitude as the displacement effected by the transformation. Application of the transformation is, therefore, still a sensible proceeding, and a linear relation can be considered to be a useful approximation. In fact, a significant improvement in agreement between two systems appears after application of the calculated linear transformation. In the case of the B→M relation, thanks to the transformation, the B system moves toward a position within the limits of the S,M,F group.

At this point, one might speculate whether it would be feasible to set up formulas which could transform any given system into a compromise system which forms the mean of the given systems. Thus, different investigators could still use the systems they prefer, but the results would become generally comparable. Such a compromise system would probably also imply a compromise between the views of strict homogeneity and marked heterogeneity in conductivity of the trunk. Standardization in vectorcardiography is necessary, but unacceptable to many if this implies the imposition of an arbitrary system. The introduction of a compromise system might meet this objection and bring concordance nearer.

Summary

If it were assumed that the electrical action of the heart could be described as that of a stationary dipole, one could show that a VCG system I could be

Table I

Transformation (or comparison)	∂	*D*	Δ	*Subjective rating*	
				Frontal	*Horizontal*
B→S	—	—	—	6.9 ± 0.09	5.6 ± 0.12
B→M	0 35	0 50	0 44	6.9 ± 0.10	5.8 ± 0.10
B→F	0 31	0.41	0 47	7.2 ± 0.10	6 0 ± 0.12
S→F	—	—	—	7.6 ± 0.05	6.8 ± 0 07
M→F	0 18	0.21	0 31	7.8 ± 0 07	7.4 ± 0.08
M→S	0 22	0.19	0.31	8 8 ± 0.07	7.8 ± 0.07

∂ and D are relative measures, defined in different ways, of the difference which exists between any two VCG systems. This difference equals the average relative displacement effected by the average transformation calculated for the two systems. Δ is a measure of the scattering of the results of the average transformation around the target system. In the subjective rating of the agreement between two systems, use is made of a scale of 0 to 10.

in the cases in which individual transformations are applied, the scattering of the results around the target will be much smaller. That the extent of the scattering in these cases is insignificant is illustrated in Table II.

The previous theoretical reasoning can be tested in practice by applying a transformation to a system and comparing the result with the target system (see page 671). For this test the B→M transformation was chosen. Vectorcardiograms were made on 136 persons, utilizing the B, M, and B→M systems. The subjective evaluation of the agreements yielded the ratings shown in Table III. Examples of the procedure are given in Fig. 3. From these ratings it is apparent that an improvement in agreement was gained, due to the transformation. The B→M system has now attained a position within the limits of the S,M,F group. The performance of the transformation is at times quite striking: something amounting to a real metamorphosis may change a disheartening dissimilarity into an encouraging degree of resemblance (Fig. 4).

Conclusions

The subjective judgment that the vectorcardiographic systems, S, M, and F show good mutual agreement, and that the B system stands somewhat apart, was confirmed by means of the objective criteria ∂ and D, which are expressions of the extent of the operation necessary to transform one system into another. The cleft between the group formed by the S, M, and F systems and the B system is probably related to the postulation of homogeneous conductivity of the human torso in the former and of a considerable measure of heterogeneity in the latter.

Individual transformations, which are calculated separately for each subject, are very accurate, i.e., there is negligible scattering (Δ) of the transformed system around the target system. This constitutes an argument for the assumption, in the individual case, of a stationary dipole, which, in turn, justifies the use of a linear transformation. However, one must remain cognizant of the fact that the theorem, "given a stationary dipole, all relations are linear," may not be inverted. In fact, a VCG loop, or, in general, a geometrical figure, can always be transformed with only slight scattering into another VCG loop or geometrical form by means of linear equations, *provided that both figures have a simple and smooth shape.* This is independent of the question whether the origin of the vectorcardiogram is a single stationary dipole or a more complicated generator.

The *average* transformation calculated for a large group shows a much larger scattering than the *individual* one. This means that a linear relationship no longer covers the relation between two systems. The relation between heart vector and leads appears to vary appreciably from individual to individual, and the assumption of a stationary dipole is no longer completely valid: higher poles will assume significance when data obtained from one

Case reports

Pericarditis due to histoplasmosis

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In 1906, Darling[1] initiated clinical knowledge of histoplasmosis when he reported the presence of intracellular organisms in disseminated lesions found at autopsy. He believed that these intracellular organisms were Protozoa, and 30 years passed before DeMonbreun[2] demonstrated the fungal character. Histoplasmosis was considered to be a rare and fatal disease until 1945, when Christie and Peterson[3] established a relationship between histoplasmin sensitivity and nontuberculous pulmonary calcification. Histoplasmosis is now known to be widely endemic and even epidemic.[4] The active forms of disseminated or pulmonary disease affect almost exclusively the white race, the male sex, and persons in the extreme limits of age. Histoplasmosis involves primarily the reticuloendothelial system, with widespread lesions in the liver, spleen, lungs, lymph nodes, bones, and gastrointestinal tract.[5] Since lesions have been reported in the mediastinum,[6] myocardium,[7] and endocardium,[8] it is not surprising that the pericardium should be affected.

Billings and Couch,[9] in 1955, reported on 2 patients with calcification of the pericardium who had positive histoplasmin skin tests but negative tuberculin tests, and suggested that histoplasmosis might be responsible for the pericardial calcification. Additional cases of pericarditis or pericardial calcification have been published by McNerney,[10] Hurwitz and Pastor,[11] and Lamb.[12] Positive histoplasmin skin tests and the absence of other positive skin tests provided presumptive evidence of the histoplasmosis etiology. In 1961, Wooley and Hosier[13] operated on a 14-year-old girl who had constrictive pericarditis, and demonstrated by smear *Histoplasma capsulatum* in the constrictive peel. More recently, Gregoriades, Langeluttig and Polk,[14] of Mt. Vernon, Missouri, reported a case of pericarditis with massive effusion, with—for the first time—culture of the Histoplasma organism from the fluid. In view of a limited experience of 5 presumptive cases and 2 proved cases of pericarditis due to histoplasmosis, the following cases—one presumptive and one proved—are thought to be of interest.

Case reports

Case 1. J C McC (#34493), a 10-year-old white boy, was first admitted to the University Hospital on June 25, 1958, with a 2-month history of progressive abdominal enlargement, anorexia, increased fatigability, and mild dyspnea on exertion. He had a brief respiratory illness with low-grade fever, and pleuritic pain in the left anterior side of the chest.

Previous routine examinations had detected a soft systolic murmur at the apex, but the heart was normal in size, the blood pressure was 110/70 mm Hg, and blood counts were normal. His past history and development otherwise were not remarkable.

Physical examination showed a thin, fairly well-developed boy with no skin lesions or palpable lymph nodes, but moderate distention of the neck

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system K by means of a set of three linear equations. In these equations, each coordinate of a general point of K is expressed in all three coordinates of its corresponding (i.e., isophasic) point of L:

$$X_K = p_x X_L + q_x Y_L + r_x Z_L$$
$$Y_K = p_y X_L + q_y Y_L + r_y Z_L$$
$$Z_K = p_z X_L + q_z Y_L + r_z Z_L$$

The values X_K, Y_K, Z_K and X_L, Y_L, Z_L can be found by measuring the coordinates of a pair of isophasic points of a loop K and a loop L in a single individual. To be able to calculate the nine unknown coefficients p_x . . . . . r_z, two more sets of three equations are required, which can be obtained by measuring the coordinates of a second and third pair of points. Individual transformations of this kind have been calculated in a limited number of patients for the following four systems: Frank (F), Schmitt III (S), McFee (M), and Burger (B). In this way, good adaptation was possible, showing that in the individual case the assumption of a stationary dipole is a good working hypothesis. However, in order to obtain a single transformation that ensures for each individual case, on the average, the best possible adaptation, an *average* transformation must be determined. This may be calculated from a sufficiently large number of individual transformations. It is easier, however, to pool all equations which pertain to each vector component from all experimental subjects, and then to carry out a single calculation, using the method of least squares. In 169 individuals, transformations were calculated in this manner for the relations B-M, B-F, M-F, and M-S. The formulas are presented in the paper. With the help of the transformations it is also possible to quantitatively formulate the degree to which two systems disagree. These values were found to be in reasonable agreement with the ratings assigned by means of subjective evaluation to the degree of correspondence shown by each pair of systems. The M, S, and F systems satisfactorily resemble each other. The B system shows a lack of agreement with this group, possibly because of the postulation of electrical heterogeneity of the human trunk in this system. The validity of the transformation method was subsequently tested in 139 persons from whom vectorcardiograms were obtained according to systems B, M, and B-transformed-to-M. Owing to the transformation a marked improvement in agreement was gained: the B system now lay within the limits of the M,S,F group. Any well-founded VCG system might in this manner, while maintaining its characteristic electrode arrangement, be adapted to any other system desired.

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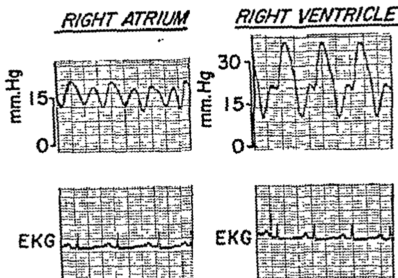


Fig. 2 Pressure tracings from the cardiac catheterization in Case 1, showing a high right atrial pressure, failure of the right ventricular diastolic dip to reach zero, and the high end-diastolic pressure in the right ventricle.

normal vigor and activity, but returned to Little League baseball by the following summer. Continued re-examinations through May, 1962, showed that the heart was still enlarged, although the vascular markings appeared to be within normal limits. The liver was not palpable, and there was no ascites or edema. The electrocardiograms were within normal limits, and repeat complement fixation tests remained negative.

COMMENT. The clear-cut documented history of the febrile episode and anterior chest pain suggests that this boy had acute pericarditis 4 months prior to the development of symptoms of constrictive pericarditis. The positive histoplasmin skin tests and negative tuberculin tests are presumptive evidence that histoplasmosis was the etiological agent.

Case 2. J.T.B., a 49-year-old white male farmer, was admitted to the Mississippi State Sanatorium on Sept. 24, 1959, from the north central portion of the state, where histoplasmosis is extremely prevalent. One month prior to admission the patient had developed an acute lower respiratory infection, with fever, general malaise, cough productive of a large amount of greenish-yellow sputum, anorexia, and a 10-pound loss of weight. An x-ray film 3 weeks prior to admission revealed an infiltrate in the right upper lung field, but several sputa were reported to be negative of *Mycobacterium tuberculosis*. The review of systems was essentially negative.

Physical examination showed a well-developed, well-nourished man who was not acutely ill. The right upper chest showed impaired resonance, with increased tactile and vocal fremitus, moist râles, and cavernous breathing. The heart sounds were clear, with no murmurs, thrills, or adventitious sounds. Blood pressure was 130/80 mm. Hg, and pulse was 80. The abdominal examination was negative, and there was no edema, cyanosis, or clubbing.

Laboratory data revealed normal urine, serology, and stool. The red blood cell count was 5.1 million, and the white blood cell count, 10,200 with a normal differential. Hemoglobin was 14.5 Gm. Blood sugar was 82 mg. per cent. The blastomycin, coccidioidin, and tuberculin skin tests were negative, but the histoplasmin produced a reaction of 15 mm. Several cultures of the sputa and gastric washings were negative for tubercle bacilli and fungi.

The initial chest x-ray films showed a dense infiltrate in the right upper lung field, with several cavities.

The patient was continued on isoniazid and PAS because of the presumptive diagnosis of tuberculosis. Because the x-ray films showed minimal change after 4 months of therapy, the patient was scheduled for resection for the right apical disease, both for therapy and for diagnosis.

Bronchoscopy on March 12, 1960, was completely normal, and the bronchial washings were negative for acid-fast bacilli, fungi, and tumor cells. On March 17, 1960, a right thoracotomy revealed a

Table I. Cardiac catheterization data for J.C.McC.

Site	*Pressure (mm. Hg)*	*Mean*
SVC	22/12	17
RA	21/10	15
RV	40/24	25
PA	33/16	20

Cardiac output 3.0 L./min.
Cardiac index 2.6 L./min./M.² BSA





Fig. 1. A and B (For legend see opposite column.)

veins. The lungs were clear. The precordium showed prominent cardiac pulsations, and the heart was enlarged to the left. Heart sounds were clear except for an inconstant high-pitched systolic murmur which varied with position and respiration. The blood pressure was 100/60 mm. Hg; the rhythm was regular at a rate of 110. The upper abdomen was markedly protuberant, with the sharp, firm edge of the liver being easily palpable 3 cm. below the costal margin. There was no peripheral edema, clubbing or cyanosis.

Laboratory data revealed a hematocrit of 43, and a white blood cell count of 7,550 with a normal differential. Platelet count was 185,000. Urinalysis and serology were negative. Corrected sedimentation rate was 0. Total protein was 7.7, albumin 5.8, and globulin 1.9 Gm. Bilirubin was 1. Thymol turbidity was 1.3, and glucose 96 mg. per cent. The electrocardiogram showed low T waves, with sagging of the S-T segments compatible with, but not specific for, pericarditis. Chest x-ray films showed enlargement of the left atrium, right ventricle, and main trunk of the pulmonary artery.

Cardiac catheterization on July 2, 1958, revealed the pressures shown in Table I. The right ventricular curves were characterized by failure of the initial diastolic dip to reach zero, and by a high end-diastolic pressure which was approximately 60 per cent of the systolic. There was no significant gradient from the right ventricle to the pulmonary artery. Skin tests made at this time revealed a very strongly positive histoplasmin skin test, but negative blastomycin, coccidioidin, and PPD tests.

The patient was rehospitalized on July 20, 1958, for surgery. Physical examination was essentially as before, except that the liver was down 5 fingerbreadths, and a fluid wave and shifting dullness were present. There was no peripheral edema. The patient made a marked response to mercurial diuretics, losing from 77 to 71 pounds prior to operation. Complement fixation tests were negative.

At operation on July 22, 1958, the pericardium was found to be adherent and extremely thickened, particularly over the left ventricle and the left atrium, with marked calcification over both atria which extended into the left atrial wall. An extensive pericardiectomy was performed without difficulty. The postoperative course was uneventful, and the patient was discharged on the fifteenth postoperative day in good condition, with a weight of 68 pounds.

Pathologic examination of resected pericardium showed only a chronic, nonspecific pericarditis with fibrosis and calcification. No organism was demonstrable and cultures were negative.

The boy required several months to return to

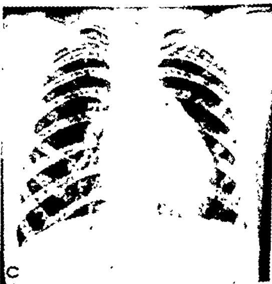


Fig. 1. Chest roentgenograms in Case 1. Posteroanterior (A) and oblique (B) views on first admission which show an enlarged heart with calcification in the region of the left atrium. C, Film of Nov. 11, 1961, 28 months postoperatively, which shows no appreciable change in cardiac contour.

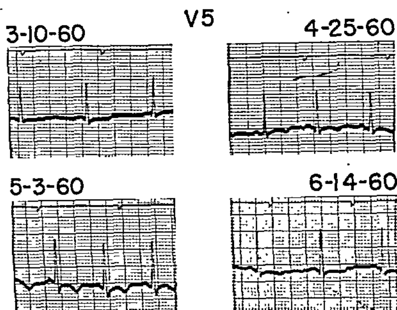


Fig. 4. Lead V_5 of the electrocardiogram in Case 2 *March 10, 1960*, Preoperative state. *April 25, 1960*, Pericardiocentesis. *May 3, 1960*, Initial amphotericin-B therapy. *June 14, 1960*, After 6 weeks of drug therapy. Subsequent electrocardiograms at completion of therapy showed no further change. Only Lead V_5 is reproduced because it showed the most definitive changes and the other leads add nothing further.

to a total dosage of 2,140 mg. During the last month of treatment the blood urea nitrogen rose to 29 mg per cent, but this gradually subsided after discontinuance of therapy. The patient developed several areas of thrombophlebitis and had several episodes of chills and fever, which usually responded to aspirin and Benadryl.

The x-ray film showed that the heart was progressively decreasing in size, and by June 14, 1960, after 6 weeks of therapy, the electrocardiogram showed reversion of T waves toward normal. The serologic tests are summarized in Table II, showing the positive complement fixation to histoplasmin antigen 2; this became negative after therapy. An additional study made on May 23, 1960, by Joseph H. Schubert, Microbiologist Section Chief, at Chamblee, Georgia, revealed the complement fixation test to be negative for the mycelian phase but showed a positive yeast phase 1:32 and coccidioidin 1:8. The agar gel precipitin was positive for both histoplasmin and coccidioidin. He noted, "It is interesting that after therapy the yeast phase titer did not change; whereas, the coccidioidin did. It is possible that the patient had a double infection. We have done numerous tests on positive sera, but have not as yet obtained a cross reaction in the precipitin test."

The patient was discharged on Aug. 24, 1960, and has been followed as an outpatient. He returned to farm work in the spring of 1961, with only minimal dyspnea on exertion. At the last visit in May, 1962, there was no evidence of pericardial constriction and his x-ray films were stable.

COMMENT. This is the first proved case of pericarditis in which an effusion developed during the course of chronic pulmonary histoplasmosis. It is not certain whether the dissemination was a sequel to the pulmonary resection. Histoplasmosis does not usually cross tissue planes, and the pericardium had not been opened. In addition, the preoperative electrocardiogram, in retrospect, showed changes compatible with early pericarditis, particularly since the post-therapy electrocardiogram showed reversion of the S-T and T-wave changes to a more normal pattern.

Table II. Summary of serologic tests in J.T.H.

Date	Histoplasmin		Coccidioidin
	Antigen 1	Antigen 2	
Nov. 16, 1959	Negative	1:32	Negative
April 18, 1960	Negative	1:8	1:64
May 9, 1960	Negative	1:16	1:16
May 16, 1960	Negative	1:32	1:8
May 23, 1960	Negative	1:32	1:16
June 27, 1960	1:16	1:16	—
Jan. 23, 1961	Negative	Negative	—

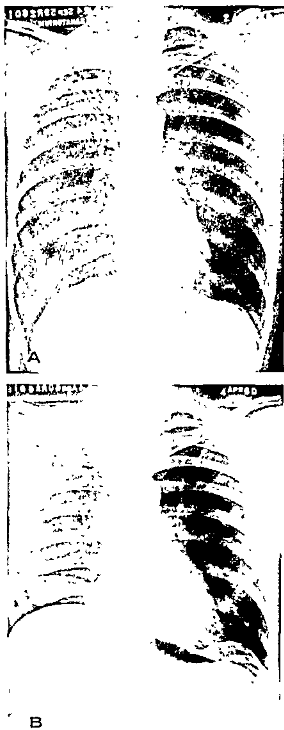


Fig. 3 *A* and *B* (*For legend see opposite column*.)

large cavity in the apex of the right upper lobe, with dense fibronodular disease in both the posterior and anterior segments and also in the middle lobe. The right upper and the right middle lobes were easily resected. The pericardium was not opened during the procedure. Pneumoperitoneum was started postoperatively and continued for approximately 3 months.

Pathologic examination of the lung revealed a thick, scarred pleural surface with yellowish plaques The largest cavity measured 3 by 3 by 2 cm. and was lined by a grayish-brown, fairly smooth membrane. The bronchi had markedly thickened walls. Scattered throughout the specimen were numerous small nodules which measured up to 8 mm. in diameter, and which were composed of caseous material. Microscopic examination revealed fibrocaseous lesions, and smears and cultures from the lung tissue showed *Histoplasma capsulatum*.

The patient's initial postoperative course was benign, but a chest x-ray film on April 20, 1960, 5 weeks postoperatively, suggested that the heart was increasing in size and had a globular shape. On April 25, 1960, the patient's temperature began to spike to 101° F. The heart showed a friction rub which was accentuated during inspiration. The preoperative electrocardiogram had shown flattening of the T waves throughout, with nonspecific S-T changes. The electrocardiogram on April 25, 1960, showed the T waves to be flattened to inverted in all leads, compatible with pericarditis. On May 3, the electrocardiogram showed further inversion of the T waves.

On April 27, 1960, pericardiocentesis yielded 30 c.c. of pink-tinged, slightly turbid fluid. Smears of this revealed *Histoplasma capsulatum*, although the cultures were negative. The patient was started on amphotericin-B, with an initial dose of 15 mg. on May 2; this was increased to a maximum of 0.7 mg. per kilogram or 50 mg. three times a week. Treatment was extended over a period of 14 weeks

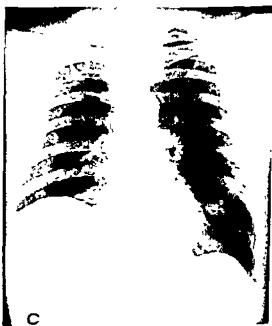


Fig. 3. Chest roentgenograms in Case 2. *A*, On admission. *B*, Three weeks after resection of the right upper and middle lobes, showing slightly enlarged contour of heart. *C*, Four months after discharge, showing normal cardiac silhouette.

blood the infusions can be given every other day. The initial dose may range from 10 to 25 mg.; this is increased gradually to 1 mg. per kilogram, although usually it does not exceed 75 mg. daily in the adult. A total dosage of approximately 2.5 Gm. has been recommended. Amphotericin-B can be instilled locally into abscesses, areas of osteomyelitis, effusion, lymph nodes, etc., according to Seabury, and is found to be fungicidal in large doses. In vitro testing by Littman, Pisano and Lancaster[26] has demonstrated that the fungi can become resistant to amphotericin-B, and one of the patients with disseminated histoplasmosis who was reported on by Yates had a clinical course which suggested an increase in resistance in the organism to the second course of therapy.

Summary

Two additional cases of pericarditis due to histoplasmosis, including the second known case of constrictive pericarditis, have been reported. This makes a total in the available literature of 3 proved cases, and 6 cases which are presumptive because of positive histoplasmin skin and/or serologic tests in patients with anergy to tuberculin.

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Discussion

The case of pericarditis with massive effusion reported by Gregoriades, and our case of pericarditis with effusion are the only two cases of pericarditis known to date to have been treated with amphotericin-B. In both, this therapy was quite effective. Neither in the case of pericardiectomy reported by Wooley and Hosier nor in our case of decortication was specific antifungal therapy administered. However, the development of acute pericarditis after pulmonary resection in our second patient suggests that, as in tuberculosis, there may be danger of dissemination of disease after surgery, and protection with antifungal drugs would be most important.

The case reported here of constrictive pericarditis with calcification must be considered to be a presumptive case, since it was not possible to demonstrate the organism by culture, smear, or histologic technique. The skin test is of great aid in the diagnosis, particularly in those areas in which the natural prevalence of the disease is low. In the mid-Mississippi Valley, where the incidence of positive skin tests may approach 70 to 90 per cent, a positive skin test is to be expected and does not establish the presence of clinical histoplasmosis any more than clinical tuberculosis is proved by a positive tuberculin test. The serologic tests often are positive only during the acute phase, but do afford a useful guide both in diagnosis and prognosis. A continuing positive titer or a rising titer suggests a poor prognosis. Conversion of the histoplasmin skin test or the development of a positive complement fixation titer would seem to be of as great a significance in histoplasmosis as is conversion of a tuberculin test in tuberculosis.

The diagnosis of pericarditis is quite difficult, particularly in the chronic stage, when only the residuals of calcification or constriction remain. Effler and Proudfit[15] utilized pericardial biopsy in 22 patients with chronic pericarditis but were able to make a specific etiological diagnosis in only 6 cases. In 2, the cultured pericardial tissue yielded tubercle bacilli, and in 1, *Streptococcus viridans;* 2 had metastatic disease, and 1 had a true chylopericardium. Eight patients showed a chronic hemorrhagic pericarditis of undetermined etiology, and the others showed no diagnostic clues. The literature contains many speculations in regard to pericardial calcification and constrictive pericarditis, with opinions that vary widely depending on individual experience.[16-20]

Since histoplasmosis mimics other diseases, particularly tuberculosis, its widespread distribution was not recognized until tuberculosis became less frequent and sensitivity studies and methods of culture became widely available. In addition, it has been estimated that approximately 25 per cent of the patients in the sanatoriums who have active histoplasmosis have coexistent tuberculosis.[21] Thus, it is not surprising that histoplasmosis only very slowly became recognized as a major medical and public health problem. It is estimated that perhaps one fifth of this country's entire population is now affected, and that as many as 500,000 new infections develop every year.[22]

Treatment. Several recent studies, including those of Seabury,[23] Smith,[24] and Yates,[25] have demonstrated the efficacy of amphotericin-B therapy in active histoplasmosis. Since it is primarily suppressive rather than fungicidal, a prolonged course is necessary. Nearly all patients demonstrate a variety of toxic manifestations, including anorexia, nausea, vomiting, chills, fever, headache, anxiety, flushing, and renal toxicity. The immediate reactions are minimized by the concomitant use of antihistaminic and antipyretic drugs or small doses of corticoids administered in the infusion. In most patients the blood urea rises to levels of 15 to 35 mg. per cent, but promptly returns to normal level after discontinuance of the drug. Likewise, amphotericin-B causes a high incidence of phlebitis. No particular liver toxicity has been observed, although occasional drops in hemoglobin have been encountered. One death has been reported, which was thought to be due to amphotericin-B toxicity in an extremely ill patient who developed an exfoliating dermatitis and acute hepatic enlargement.[26]

The drug is usually administered intravenously because of poor absorption from the intestinal tract or intramuscular injections. Because of prolonged levels in the

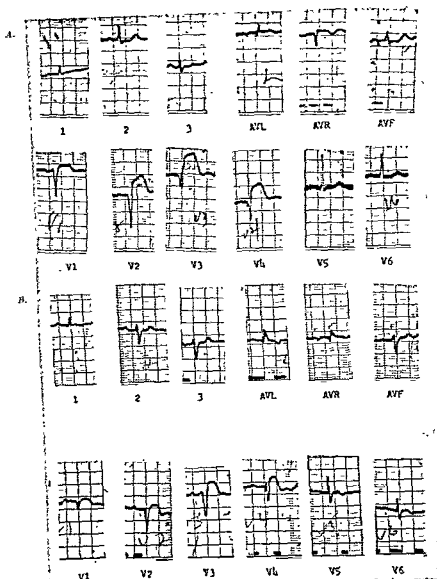


Fig. 1 Electrocardiograms before (A) and 16 days after (B) perforation of the infarcted septum, showing ÂQRS change from +40 to −70 degrees.

The patient died in intractable pulmonary edema on the twenty-third hospital day.

At necropsy the heart weighed 400 grams, and there was neither hypertrophy nor dilatation of any chamber. The papillary muscles and chordae tendineae were intact, as were all valve leaflets. The anterior descending branch of the left coronary artery was thrombosed. There was a 5.5-cm. aneurysm involving the apical anterior wall of the left ventricle, with a 0.9-cm. perforation of the adjacent interventricular septum (Fig. 3). A dumbbell shaped clot, 2 cm. wide at the ends, joined the ventricles through the perforation. The lungs weighed 1,400 grams and were edematous, with extreme vascular congestion and recent tracheobronchitis. There were no other significant pathologic findings.

Discussion

Phonocardiographic and electrocardiographic evaluation of patients with ventricular septal defect has, to date, been limited largely to those with congenital heart disease. The murmur in these cases is usually holosystolic.[9-11] A similar murmur was noted in 96 per cent of all reported cases of perforation of the infarcted interventricular septum in 1959[12]; no mention was made of the character of the murmur in the other 4 per cent. Since then, less than a dozen new cases have been reported,[4,7,13] and the murmur was holo-

Rupture of the infarcted ventricular septum

Report of a case with unusual phonocardiographic and electrocardiographic findings

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Rupture of the interventricular septum occurs in approximately 0.5 to 1 per cent of all transmural myocardial infarctions.[1] Over 110 cases have been reported in the English literature.[2] The clinical[3,4] and hemodynamic[5,6] data from these cases have been well analyzed. Confirmation of the cardiac sounds by phonocardiography, however, has rarely been reported[7,8] because of the high and early mortality due to septal perforation.[2] The following case is presented because of interesting and hitherto undocumented phonocardiographic and electrocardiographic findings.

Case report

A 65-year-old white man was admitted to The St. Vincent's Hospital of the City of New York because for 4 days he had had constant chest pain which radiated to both arms. He had no previous history of cardiac disease, and routine physical and electrocardiographic investigation 2 years earlier had been normal. On admission to the hospital he had a blood pressure of 114/86 mm. Hg, and a regular pulse of 72 per minute. His lungs were clear to percussion and auscultation. Cardiac sounds were of good quality, with regular rhythm. There were no murmurs, thrills, or heaves. Laboratory studies included an SGO transaminase of 94 units, a white blood cell count of 15,000 per cubic millimeter, with 80 per cent polymorphonuclear leukocytes and 1 band forms, and a sedimentation rate of 13 mm. per hour. The admission electrocardiogram (Fig. 1,A) showed QRS and ST-T changes consistent with acute anteroseptal myocardial infarction.

On the fourth hospital day the patient suddenly became disoriented and diaphoretic. The blood pressure was 80/60 mm. Hg, and the cardiac rate was 110 per minute. A systolic thrill was felt over the left precordium. On auscultation a Grade 5/6, harsh systolic murmur was heard over the entire precordium. It radiated into the left axilla but was loudest in the fourth intercostal space to the left of the sternum. There was no diastolic murmur. The second sound was not audible. Three days later, however, the second sound was heard clearly, and remained so until the patient's death. An auscultatory gap was noted between the end of the systolic murmur and the second sound. On the phonocardiographic tracing (Fig. 2) a long, decrescendo, systolic murmur vibration was recorded maximally at the left sternal border, in the fourth intercostal space. The murmur ended approximately 0.05 second before the onset of the second sound, which in this area was diminutive and showed no definite splitting.

Over the next 19 days the patient was moribund. The blood pressure was maintained with increasing doses of vasopressors. The blood urea nitrogen rose from 22 to 180 mg. per cent. Signs of progressive left heart failure with repeated episodes of pulmonary edema appeared. Serial electrocardiograms demonstrated a gradual change in the mean electrical ÂQRS from plus 40 degrees on the day of admission (Fig. 1,A) to minus 70 degrees on the last tracing recorded on the twentieth hospital day (Fig. 1,B). Concomitantly with this progressive left axis deviation a predominant Q in Lead aV_R evolved into a qR pattern, and a deep S developed in Leads V_5 and V_6.

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If patients with congenital ventricular septal defect develop a significant degree of pulmonary hypertension, the characteristic holosystolic murmur may change. A decrescendo murmur of small intensity and confined to the first third or half of systole is usually recorded,[9-11] and may indeed be absent if a balanced shunt develops. The patient reported on developed progressive left heart failure and, eventually, intractable pulmonary edema. The electrocardiographic changes lend credence to the concept of progressive pulmonary hypertension.

These changes are suggestive of biventricular overloading and have been well described in congenital ventricular septal defects.[14] To our knowledge, such a pattern has not previously been documented in acquired ventricular septal defects.

A second consideration is based on the fact that 90 per cent of congenital ventricular septal defects are in the membranous septum, and the murmur is almost invariably holosystolic. With congenital defects in the muscular septum, however, a short systolic murmur has been noted, and ascribed by Leatham and Segal[15] to closure of the defect as systolic contraction progresses.

An alternate explanation in our patient is that the dumbbell-shaped clot could also have sealed the septal defect as systole progressed.

Further investigation of this patient by intracardiac phonocardiography or cardiac catheterization was inadvisable.

Summary

A patient with perforation of the infarcted ventricular septum, but without the characteristic holosystolic murmur, is presented. A previously undocumented electrocardiographic pattern is presented. Various explanations for these findings are discussed.

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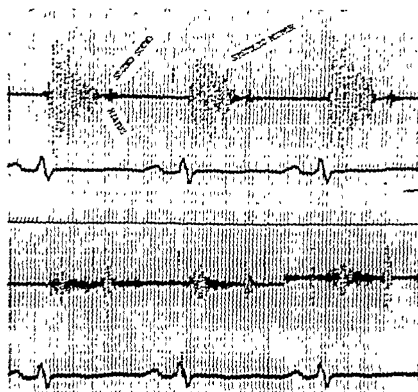


Fig. 2. Phonocardiographic tracings from the fourth intercostal space, left sternal border (above) and Erbs point (below), with 0.05 second hiatus between the end of the systolic murmur and the second sound.

systolic in all but *one* instance. That patient had "a large systolic murmur with a small gap before the second sound"[12]; although a phonocardiogram had been taken, it was not published.

At least five conditions might possibly cause a foreshortening of the systolic murmur in patients with postinfarction ventricular septal defect. These are: (1) a significant degree of coexistent pulmonary hypertension; (2) closure of a defect in the muscular septum as systolic contraction progresses; (3) mechanical sealing of the defect by a mobile clot on the ventricular septum; (4) production of balanced left and right ventricular pressures by a defect so large as to result in a single ventricle effect; and (5) location of the defect in the posterior septum so that the murmur is not audible on the anterior chest wall.

The last two considerations are eliminated in the present case by the postmortem findings. The first three factors, however, are plausible explanations both alone and in combinations.



Fig. 3. Necropsy heart specimen. Mobile thrombus partially covers the interventricular septal defect.

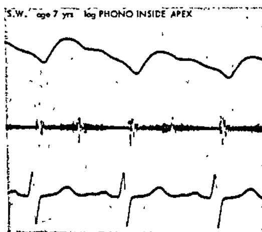


Fig. *1*. See text.



Fig. *2*. Chest x-ray film. See text.

left-to-right shunt was reduced to 15 per cent.

Curves obtained after inhalation of hydrogen using a platinum-electrode catheter according to the method of Clark[4] are reproduced in Fig 6. The top curve was obtained with the tip of the catheter in the pulmonary artery and showed the appearance of hydrogen 1.8 seconds after the gas had been inhaled. The second curve was obtained with the tip of the catheter just below the pulmonary valve, and showed the hydrogen appearing 7 seconds after it had been inhaled. This indicated that the shunt was into the pulmonary artery, and not into the outflow tract of the right ventricle.

A retrograde aortogram was obtained by injecting through a side-holed catheter situated in the noncoronary sinus of Valsalva. The lateral angiograms showed the large dilated right coronary artery, the absence of a left coronary artery arising from the aorta (Fig. *7,A*), and the subsequent filling of the left coronary artery by large collateral vessels (Fig. *7,B*), with eventual entry into the pulmonary artery (Fig. *7,C*). Anteroposterior projections are illustrated in Fig. *7,D-F*), showing the extensive communications between the right and left coronary arteries.

Despite the denial of symptoms by the girl and by her family, her working capacity on a bicycle ergometer was only 70 per cent of the average for her age and size.

The operative approach was through a median sternotomy incision, and this gave excellent visualization of the dilated right coronary artery and the anastomotic branches (Fig. 8). The left coronary artery appeared to arise entirely from the pulmonary artery, behind the posterior cusp of the pulmonary valve. It was noted that the apical area of the left ventricle was paler than normal. Because of the tremendous vascularity of the area and the thin-walled nature of the vessels, the decision made was not to attempt to join the left coronary artery to a systemic vessel. The left coronary artery was doubly ligated and transfixed near its origin at the pulmonary artery. After the operation, the continuous murmur disappeared, but an apical systolic murmur remained. The electrocardiogram showed no change. There was no rise in serum glutamic oxalacetic transaminase after this ligation The postoperative course was uneventful.

Discussion

In this asymptomatic patient, a left coronary artery which arose from the pulmonary artery was discovered when the child was referred because of a heart mur-

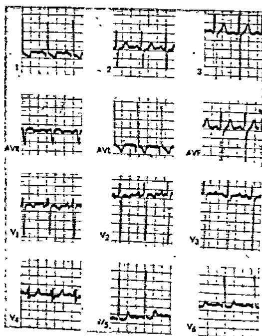


Fig. *3*. Electrocardiogram. See text.

Anomalous origin of the left coronary artery from the pulmonary artery, functioning as a coronary arteriovenous fistula

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The clinical picture of anomalous origin of the left coronary artery from the pulmonary artery in infants was first described by Bland, White and Garland.[1] Keith[2] has recently reviewed the subject. Although most individuals in whom the left coronary artery arises from the pulmonary artery die early in infancy, some survive and may remain active and asymptomatic for many years.

George and Knowlan[3] reviewed the case records of 13 adult patients with anomalous origin of the left coronary artery from the pulmonary artery, and added another case report. In most of these cases the right coronary artery was tremendously enlarged and its branches freely anastomosed with the branches of the left coronary artery. In this situation, as first postulated by Brooks,[4] the flow in the left coronary artery is in a retrograde direction, and the functional effect is similar to that of other types of coronary arteriovenous fistulas.

This report concerns a 7-year-old girl who was subjected to a detailed cardiac study which showed that the left coronary artery arose from the pulmonary artery.

Case report

S.W., a 7-year-old girl, who was 130 cm. tall and weighed 25 kilograms, was completely asymptomatic. Because a murmur had been noted when she was 5 years of age, she was referred for complete study. The apex beat suggested some left ventricular enlargement. Pulses were normal, and blood pressure was 120/60 mm. Hg. The second heart sound split normally. There was a Grade 3, high-pitched continuous murmur maximal halfway between the apex and the left sternal edge (phonocardiogram, Fig. 1). There were no other abnormalities. A chest x-ray film (Fig. 2) showed some left ventricular enlargement. The electrocardiogram (Fig. 3) was consistent with left ventricular hypertrophy and ischemia. The vectorcardiogram (Fig. 4) showed the QRS loop directed to the left, posteriorly and superiorly, and suggested left ventricular hypertrophy. The clinical diagnosis was coronary arteriovenous fistula. The findings made by catheterization of the heart are given in Table I. The pressures in the right side of the heart were normal. There was a 4 per cent increase in the oxygen saturation in the pulmonary artery. The left-to-right shunt was calculated to be 0.9 L./min.

A dye-dilution curve was obtained by injecting Cardiogreen dye into the pulmonary artery and sampling from the femoral artery through a cuvette densitometer. The curve (Fig. 5, *top*) showed a definite early recirculation hump, which indicated a left-to-right shunt. By means of the method of Carter and Wood,[5] this was calculated to be 30 per cent. A second curve (Fig. 5, *bottom*) was obtained after the patient had inhaled amyl nitrite. The

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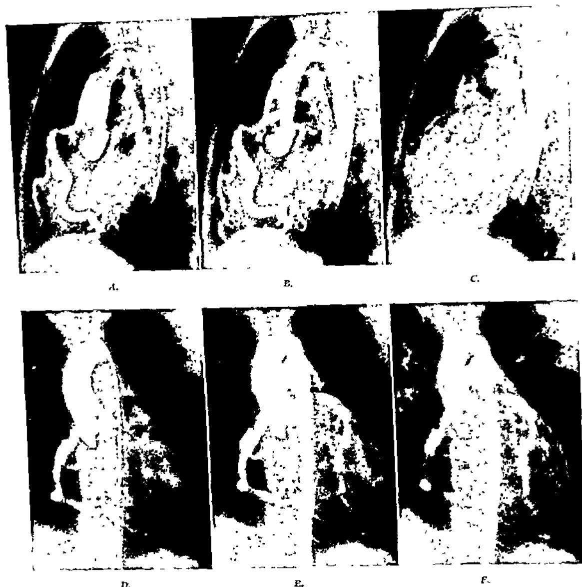


Fig. 7. Angiograms. *A-C*, Lateral projections. *D-F*, Anteroposterior projections See text.

the entire left coronary artery arises from the aorta. The shunt then goes from the right to the left coronary artery and involves the two vessels.

Most patients with this anomaly have severe left ventricular ischemia and die in the first year of life. The factors responsible for the survival of a few patients to adult life is not entirely clear, but most seem to have extensive collateral vessels which join the right and the left coronary arteries. These intercoronary anastomoses would seem to have been present from birth, for in none of the cases rep ed in adults were cardiac signs or symptoms present during the first year.

Theoretically, surgical ligation of the aberrant left coronary artery near its origin stops the runoff into the pulmonary artery of blood received by the left coronary artery from the right coronary artery. It is hoped that this will increase the perfusion of left ventricular myocardium. Case and associates,[7] and Sabiston, Neill and Taussig[8] have reported on 4 symptomatic infants who showed ent after they had undergone coronary artery near



Fig. 4. Vectorcardiograms. See text.

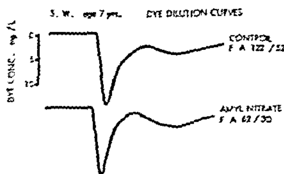


Fig. 5. Dye-dilution curves. See text.

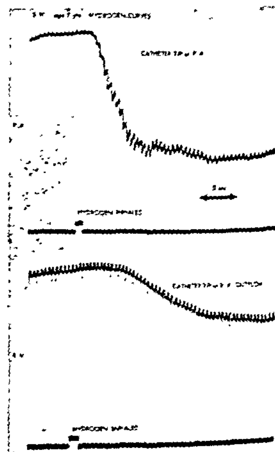


Fig. 6. Hydrogen curves. See text.

mur. The flow in the left coronary artery was in a retrograde direction, resulting in a 20 per cent left-to-right shunt from the aorta to the pulmonary artery. Although the functional effect is that of a coronary arteriovenous fistula, it is probably better to classify this lesion with other cases of left coronary artery arising from the pulmonary artery. Despite the extensive collateral circulation from the right coronary artery to the left coronary artery and its tributaries, there was electrocardiographic and direct visual evidence of ischemia of the left ventricle. Ischemia is not commonly present in the case of other coronary arteriovenous fistulas in which the two coronary arteries arise from the aorta.

The difference is probably one of degree, and the developmental origin of the two conditions would seem to be similar. In the case of a coronary arteriovenous fistula which drains into the pulmonary artery, one or more branches of the left coronary artery may arise from the pulmonary artery, still leaving a large radical arising from the aorta. The shunt involves one vessel. In anomalous origin of the left coronary artery from the pulmonary artery

Addendum

The electrocardiogram and chest x-ray film have shown no change 14 months after the operation. The left ventricle has remained overactive, and a late apical systolic murmur is still present.

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Fig. 8. See text.

Injection of opaque media into the chambers of the right side of the heart or into the pulmonary artery usually does not show filling of a left coronary artery which arises from the pulmonary artery. Keith[2] found filling from the pulmonary artery in 1 of 5 children studied. However, Stern and associates[8] reported 2 such instances

Table I. Findings made by catheterization of the heart

Chamber	Oxygen saturation (%)	Pressure (mm. Hg)
IVC	80	—
SVC	75	—
RA	76	6/2
RV	76	25/1
PA	80	22/6
Aorta	99	100/62

Oxygen consumption: 132 c.c./min.
Oxygen capacity: 18.0 vols. %
Pulmonary flow: 4.1 L./min
Systemic flow: 3.2 L./min.
Left-to-right shunt: 0.9 L./min. (22%)

and suggested that ligation of the left coronary artery might be harmful in such circumstances. Flow from the pulmonary artery into the left coronary artery may be associated with elevation of pulmonary arterial pressure secondary to left heart failure. An angiogram of the right side was not obtained in our patient.

Of the 14 adult patients whose cases were reviewed by George and Knowlan,[4] 11 died suddenly, 1 accidentally, and 1 after surgery. The mean age at death was 35 years. Only one patient had a continuous murmur. Two patients had normal physical examinations shortly before death, and one of these had a normal electrocardiogram. The clinical diagnosis was not made.

Whether the operation in the present case has altered the prognosis is, of course, not known, but patients with a single coronary artery may have a normal life span.[10,11]

In our patient, the inhalation of amyl nitrite caused a reduction of the left-to-right shunt into the pulmonary artery. It has been demonstrated that all left-to-right shunts are reduced by amyl nitrite,[12] and the shunt in this girl probably decreased because of the reduced aortic pulmonary pressure gradient produced by the amyl nitrite. Another explanation might be that the amyl nitrite caused dilatation of the coronary vessels and increased the myocardial perfusion at the expense of the flow of blood into the pulmonary artery.

Summary and conclusions

1. An asymptomatic 7-year-old girl was studied because of the presence of a continuous murmur.

2. Catheterization of the heart showed a 20 per cent left-to-right shunt into the pulmonary artery, and retrograde aortography demonstrated a large right coronary artery which filled the left coronary artery via collaterals, with the left coronary artery emptying into the pulmonary artery. The diagnosis was confirmed at operation.

3. Some instances of left coronary artery arising from the pulmonary artery may mimic coronary arteriovenous fistulas, but are best classified as anomalous left coronary arteries, since myocardial perfusion is usually impaired.

1,000 mm. per second, and near the base, about 300 to 600 mm. per second.

RIGHT SEPTAL SURFACE. The first portion of the right septal surface to be activated is the inferior one third in the region of the base of the anterior papillary muscle where the right bundle branch begins to ramify.[4,6,10,12-14] Recent studies have shown that the earliest activity on the right side is above and anterior to the anterior papillary muscle.[12] The initial activity on the right septal surface occurs about 0.005 to 0.015 sec. after the initial activation of the middle third of the left septal surface.[6,13] The right septal apex is activated 0.005 to 0.01 sec. later.[4,6] The remaining right septal surface is activated from below upward, so that the last area to be activated is the posterobasal region of the right septal surface (0.02 to 0.03 sec. after the activation of the base of the anterior papillary muscle).[4,6,14] However, Amer and associates[12] have found that the spread of activity over the right septal surface requires from 35 to 60 msec. These same workers have found, in contrast to most other studies, that the earliest activity recorded from a single point on both the right and left septal surfaces is nearly simultaneous.[12] Because of the very rapid activation on the left, a large portion of the left septal surface is excited before a comparable area on the right side is activated.[12]

It has been demonstrated in some cases that the posterosuperior portion of the right septal surface may be activated by the left bundle.[12,13] Amer and co-workers have also shown in some dogs that the most posterior portion of the right septal surface is activated normally from the free wall of the right ventricle.[12]

ACTIVATION OF THE SEPTAL MASS. Scher and associates[11,13] have found the septum to be activated from both sides toward the center, in the form of double envelopment, and the latest septal activity to be central. They found evidence that the Purkinje system does not significantly penetrate beyond the endocardial surface of the septum.[13] These workers found that, within the septal muscle, conduction proceeds syncytially, without connective tissue or other barriers, and without special control of penetrating Purkinje fibers.[13] The rate of spread through the muscular substance of the septum is about 300 mm. per second.[11,13] Scher and associates[13] noted in 60 per cent of their studies that there is dominant invasion of the septum from the left. They believe that the percentage of the thickness of the septum excited from the left or right is a function of the distribution of the endocardial Purkinje fibers, and that the preponderance of excitation from the left is due to earlier activation of the left endocardium.[13] Activity travels up the septum from apex to base, with a slower speed at the basal septal endocardium.[11] In the posterior and upper septum there is a marked tendency for the septum to be activated from the left.[13]

Septal activation is usually complete in 0.025 sec. according to Scher and co-workers.[13] Medrano and associates[16-19] have carried out extensive studies of the activation of the anterobasal, posterobasal, and the anterior, middle, and posterior portions of the middle third of the interventricular septum. They have found that, although activation may spread from both septal surfaces toward the middle, or in a few cases from the center of the septum toward both endocardial surfaces, in the majority of experiments the sense of dominant activity is from the left to the right.

Medrano and co-workers[14] have found the activation process to spread almost instantaneously through the subendocardial muscle of the middle third of the left septal surface, and believe that it is propagated through the Purkinje network. As the activation process penetrates the deeper layers of the left septal mass, its speed progressively slows.[14] This is thought to be secondary to the scarcity of Purkinje fibers in the deeper portion of the septum, and the activation process must now traverse the muscle fibers in this region.[14] The latest regions to be depolarized are in the basal septum.[4,6,9,11,14] Complexes of the QR and QRS type are found in the superior portion of the septum. The initial Q waves are the result of strong forces directed toward the apices and mid-portion of the free ventricular walls, overbalancing the upwardly directed force. As the activation wave approaches the high recording electrode, local forces dominate and a late R wave is inscribed.[14]

ELECTRICAL AND ANATOMIC PARTITION OF THE INTERVENTRICULAR SEPTUM. It has been demonstrated by Medrano and Sodi-Pal-

Review

Current concepts of ventricular activation in the normal heart, in left bundle branch block, and in left bundle branch block with myocardial infarction

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It has been nearly 50 years since Sir Thomas Lewis described the process of ventricular activation in the dog's heart,[1,2] and later in the human heart.[3] He emphasized the importance of the specialized conducting tissues, particularly the Purkinje system, in the spread of the activation process. Lewis found the earliest site of activity on the left septal surface immediately beneath the aortic valve.[1] Many of his careful observations have been confirmed by recent investigators using more refined techniques. However, Lewis's concepts[1,3] of the uniform activation of the interventricular septum from both the right and left septal surfaces and from base to apex have been challenged by some workers.[4-6]

The purpose of this paper is to review briefly the current concepts of ventricular activation based upon recent studies in the normal heart, in left bundle branch block (LBBB), and in LBBB with myocardial infarction. Most of these experiments have been performed in the dog heart and may, therefore, not necessarily represent the situation in the human heart. Ventricular activation in goats and other ruminants is different from that found in dogs and will not be considered further at this time.[7-9]

There is lack of uniform agreement among the various investigators in regard to the precise course of ventricular activation, particularly in the interventricular septum.

Activation of the normal heart

Septum.

LEFT SEPTAL SURFACE. The first portion of the left septal surface to be activated is the middle third, which is the area where the left bundle branch begins to subdivide.[10-14] The activation process spreads rapidly following the Purkinje network, which fans out over the surface. The apical regions of the septum near the anterior and posterior borders, as well as those under the aortic valves, are activated about 0.01 sec. (10 msec.) after the first portion.[6] The speed of the process is about 1,000 mm. per second.[6,13] Amer and associates[12] have found, with the exception of peripheral points at the base, that the left septal surface is activated in 10 to 15 msec.

The last region to be activated is the posterobasal portion.[14] This later activation of the basal portion of the left septal surface has been interpreted as suggesting sparseness of the Purkinje fibers in this region.[1,12,14] The conduction rates in the upper one third of the septum are fairly slow and uniform.[14] Scher and associates[13] have found the spread of activation over the lower portion of the left septal surface to be about

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left septal surface, Purkinje activity preceded activity in adjacent muscle fibers.

Activation of muscle fibers of the left septal surface is recorded first in the central area. Depolarization of the muscle fibers of the anterior, apical, and posterior septal margins is completed within 12 to 20 msec. after the initial activation of the muscle fibers of the central area. The muscle fibers at the base of the septum are depolarized later, and the latest activity was recorded beneath the aortic valve ring. The time required for activation of the muscle fibers of the left septal surface varied from 50 to 60 msec. Venerose and co-workers[25] concluded that activation of muscle fibers of the septal surface was the direct result of the spread of excitation to these fibers from the subendocardial Purkinje network.

Activation of ventricular walls.

Scher and co-workers[26] have found that the parts which are activated earliest in the ventricular walls are on the endocardial surfaces of both ventricles at the junction of the free wall and septum in the mid-anterior region. Through rapid Purkinje conduction much of the endocardium which borders the apical and central cavities bilaterally is excited within the first few milliseconds of the QRS complex. Irregular cones of active tissue surround both cavities by about a quarter of the way through the QRS complex. These eventually unite through double envelopment of the septum and gradually break through to the epicardial surface, first on the right, then anteriorly in the central and apical regions, and, finally, basally and posteriorly on the left.[11]

Scher and Young[10,31] have found that most of the endocardium is activated quite rapidly by the Purkinje system, which conducts at about 1,000 mm. per second. They believe that the apparent velocity of Purkinje conduction often exceeds this value because the fibers branch extensively.[10] They do not believe that the Purkinje system penetrates the myocardial wall. Instead they believe that the spread of excitation through the myocardium is of a syncytial nature, and that the average velocity of conduction through most of the myocardium is about 300 mm. per second.[10,26]

Durrer and associates[8,27,28] have demonstrated that the inner layers of the left ventricular wall are activated by rapidly conducting (2,500 mm. per second) Purkinje fibers which penetrate the lateral part of the left ventricular wall to a depth of about two fifths of the diastolic thickness of the wall. In these inner layers there is nearly synchronous activation[27] in an endocardial-epicardial direction.[28]

The Purkinje system delivers the wave of excitation to all subendocardial parts of the ventricles within 5 to 10 msec., according to Durrer and associates.[9]

In the outer layer only, muscle conduction is present at a rate of about 500 mm. per second.[9,27,28] There is a well-defined, somewhat irregular, wave front which is propagated continuously to the epicardial surface.[8,28] In the inner layer the wave front is nearly perpendicular to the endocardial surface[28] but also moves in an apicobasal direction.[8] Because the conduction velocity in the Purkinje system is greater than the myocardial conduction velocity, the activation front makes an angle of 5 to 10 degrees with the epicardial surface.[8,28]

Durrer and co-workers[8,28] have demonstrated that in the lateral left ventricular wall this activation front proceeds in an apicobasal direction. The last part to be activated is the posterobasal portion of the left ventricular wall near the ventricular septum.[8]

Kennamer and associates[29] found by means of intramural leads that as much as 80 per cent of the innermost ventricular wall is activated almost simultaneously, giving rise to QS complexes.

FREE LEFT VENTRICULAR WALL. The apex of the left ventricle undergoes activation about 0.0075 to 0.010 sec. after the initial depolarization of the middle third of the left septal surface.[6] From the region of the apical endocardium the impulse spreads rapidly to the entire left ventricular endocardium.[6]

According to Sodi-Pallares and associates,[30] the inner 40 to 50 per cent of the left ventricular free wall is activated almost instantaneously because of the penetration of the Purkinje system, with multiple islands or spheres of activation occurring simultaneously. The outer one half of the free wall is activated more slowly (about 350 mm. per second) by the spread of the impulse through the muscle fibers. This

lares (at least in the upper two thirds of the septum) that the bulk of the septal mass normally is activated through the left bundle, and that there are areas on the right septal surface that are activated by the left bundle.[6,14] The right septal mass normally activated by the right bundle is only about one third to one fourth that of the left.[14]

It has been further shown by these workers that the left and right septal masses are electrically independent. In other words, there is an electrical "barrier" between them. This boundary lies close to the right septal surface and is about 2 mm. in width.[4] However, this boundary is crossed (with delay) in cases of bundle branch block, as will be discussed later.

Lev[20] has demonstrated that there is an anatomic counterpart of this electrical partition of the septum. He has shown that under normal conditions the left septal mass contributes 70 to 80 per cent of the total septum (based upon the upper two thirds).[20]

SEPTAL VECTOR. The initial activation can be represented by a vector directed from left to right and pointing forward from the mid-portion of the left septal surface toward the trabecular zone and apex of the right ventricle, to the anterior papillary muscle on the right septal surface.[8,11,21] This *initial septal vector* gives rise to the normal q waves in Leads V_5, V_6 and the small r waves in Leads V_1 and V_2.[21,22] The forces produced by the lower third of the left septal mass are ordinarily not identified during normal activation because they are masked by the electrical dominance of the free left ventricular wall.[22]

Later, a *second septal vector* (third cardiac vector) is directed upward, backward, and toward the right, corresponding to the late activation of the basal portion of the septum.[6,10,11,21,22] The *mean* or general vector of septal activation can be represented as being directed from left to right, from below upward, and from front to back.[5,14]

Purkinje tissue.

The distribution of the Purkinje tissue in the heart has been well described anatomically.[3] This has been confirmed by recent studies of the Purkinje potential.[24,25] On the left side of the heart, Purkinje tissue is found in the middle and lower third of the septum, the apex of the left ventricle, and the papillary muscles. Purkinje potentials have been recorded up to a depth of 5 mm. in the middle third of the left septal mass, and up to 4 mm. in the middle third of the lateral portion of the left ventricular free wall.[24] No Purkinje potentials were recorded at the base of the interventricular septum or the basal regions of the left ventricle.

On the right side of the heart, Purkinje tissue is found in the region of the middle third of the right septal surface, the anterior papillary muscle, the apex, and the trabecular zone. Purkinje potentials have been recorded only in the trabecular zone near the interventricular septum in the dog by Medrano and associates.[24] These same workers believe, however, that there is more extensive ramification of the right Purkinje network in the human heart.[24]

The period of latency between activation of Purkinje tissue and the adjacent muscle fibers is the same for both sides of the heart.[24] The earlier activation of the left septal surface does not occur at the level of the Purkinje fibers but is a result of the distribution of the first ramifications, which are higher on the left bundle than on the right.[24]

Venerose and associates[25] have recently made some important observations concerning the sequence of activation of the Purkinje fibers and muscle fibers of the left septal surface. In the normal heart, the earliest activity recorded on the left septal surface is from the Purkinje fibers of the left bundle high on the interventricular septum over the point of emergence of the left bundle and precedes that of underlying muscle from 75 to 85 msec. This activity of the Purkinje fibers of the left bundle occurs during the P-R interval of the conventional electrocardiogram. After excitation of the Purkinje fibers of the left bundle, activity of the subendocardial Purkinje fibers of the left septal surface is first recorded in the central area of the septum. The latest activity of the subendocardial Purkinje fibers is recorded at the base of the septum beneath the aortic and mitral valve rings and occurs 30 to 50 msec. after that recorded from the central septum. The time required for activity to spread from the left bundle throughout the subendocardial Purkinje network of the left septal surface ranges from 35 to 60 msec. In every location on the

However, Scher and associates[13] believe that almost all of the prolonged duration of the QRS complex in LBBB is due to the increased time necessary to activate the septum from right to left. In more recent studies, Erickson, Scher, and Becker[32] have found (at least in right bundle branch block) that there is prolongation of the time required to activate the endocardium of the blocked ventricle. Since the velocity of the endocardial spread is normal, they attribute the prolongation to altered site of initial activity and consequent altered pattern of spread,[32] and also to the small area initially activated.[10] These workers[13] deny any "block" or "site of delay" in the septum.

According to Sodi-Pallares,[6] the activation of the free wall of the left ventricle in LBBB, although delayed in onset, proceeds in a normal manner from endocardium to epicardium.

Other workers,[10,36-40] however, contend that there is also a delay in the activation of the free left ventricular wall. It has been suggested that this delay in the mural activation may be due to an abnormal route of activation, i.e., the wave enters the mural myocardium directly without passing through the Purkinje system[40] and spreads by fiber-to-fiber conduction.[37] Bryant[38] believes that the anomalous activation of the free left ventricular wall may follow a course more parallel and less perpendicular to the endocardial and epicardial surfaces than normally, whereas others[6,39,40] favor a normal endocardial-epicardial spread of depolarization in the left ventricular free wall. Smith and associates[39] have also suggested that the delay in the left ventricular activation may be due to conduction over a lengthened (less direct) Purkinje system. These workers[39] have found the onset of left ventricular excitation in LBBB to be delayed from 0.026 to 0.040 sec. They attribute this delay primarily to the septum. In addition, however, they found that the time interval between the earliest and latest points of excitation on the left ventricle was increased by 0.012 to 0.034 sec. over the control, and suggested that the free wall as well as the septum contributed to the total delay.[39]

Becker and associates[16] have made some very interesting observations concerning the spread of the activation process in LBBB. The earliest activity occurs at the anterior border of the right ventricular cavity. During the first 15 msec. of the QRS there is depolarization of the tissue normally activated by the right bundle: the right septal and right ventricular myocardium. The septum is activated smoothly by muscle conduction from right to left, with no evidence of intraseptal delay. Since the wave front is concave, as viewed from the left, activity was found to occur on the septal portion of the anterior epicardium before it reached the left septal endocardial surface. Septal activation was found to take from 50 to 60 msec. By this time, ventricular activation had extended to both the anterior and posterior epicardium. A very interesting observation was that, with the early activation of the epicardium in the anterior septal region, there was epicardial-endocardial spread by muscle conduction. As the activation wave moved to the left, there was spread from both the epicardium and the endocardium toward the center of the wall. With the activation of the left septal surface the wave front spread endocardially and depolarization began in the free wall bordering the cavity. During the 60 to 75-msec. period the wave front moved laterally, and the impulse appeared to enter the endocardial conduction network (Purkinje network), initiating endocardial-epicardial spread with activation of most of the left lateral free wall. During the 75 to 100-msec. period the papillary muscles and extreme lateral free left ventricular wall were activated.

Medrano and associates[24] have studied the Purkinje potentials in LBBB. The interval between the potential of the bundle of His and the left Purkinje arborization was 0.020 sec. in the control and 0.099 sec. with complete LBBB. They also found the difference in time between the right Purkinje arborization potential and the left Purkinje arborization potential to be 0.072 sec. in LBBB. They concluded that this delay in conduction across the septum again suggested the presence of a physiologic septal barrier.

Venerose and associates[25] have demonstrated in LBBB that Purkinje fiber activity, although delayed in onset from 42 to 70 msec., is detected at multiple points on the left septal surface from the anterior, pos-

forms an advancing wave front which proceeds from the so-called "electrical endocardium" to the epicardium.[30]

Unipolar leads recorded from the inner portion of the left ventricular wall are entirely negative (QS).[8,27,29,30] It is only the outer shell of the left ventricular wall that gives rise to the positive complex (R wave).[8,27,29,30] The distribution of QS complexes was found to depend upon the anatomic region explored and to be absent in the basal portion of the left ventricular free wall where the Purkinje fibers are scarce or absent.[30]

The vector that represents activation of the free left ventricular wall is directed leftward, posteriorly, and either somewhat upward or downward (depending upon the position of the heart).[10,21] This vector (second cardiac vector) corresponds to the tall R waves in Leads V_5, V_6 and the deep S waves in Leads V_1, V_2.[21,23] The wave front of activation moves in an apicobasal direction over the left ventricular surface.[31] The last portion of both ventricles to be activated is the posterobasal region,[9] which, together with the basal part of the septum, contributes to the third cardiac vector, which is directed upward, backward, and to the right.[23]

FREE RIGHT VENTRICULAR WALL. The endocardial area of the apex and anteroinferior portion of the free right ventricular wall near the trabecular zone are activated from 0.005 to 0.01 sec. after activation of the base of the anterior papillary muscle on the right septal surface, and about 0.005 to 0.01 sec. after activation of the left ventricular apex.[6] Erickson and associates[32] have found that the central area of the right ventricular wall is the region activated earliest. The initial wave of depolarization of the right ventricular free wall is toward the right and toward the apex of the ventricle.[33] The remainder of the right ventricular endocardial surface is activated quite rapidly at a rate of 1,000 to 2,000 mm. per second,[32] a situation existing in the right ventricular wall similar to that described for the left ventricular wall. Because the right ventricular wall is much thinner, its activation is completed before that of the left ventricular free wall. As a consequence, the vector of the right ventricular free wall is small and can practically be ignored in the vector representation of ventricular depolarization.[21]

Activation in left bundle branch block

In complete left bundle branch block (LBBB) the first portion of the interventricular septum to be activated is the lower third of the right septal surface in the region of the anterior papillary muscle. The remainder of the right septal surface is activated in a normal manner from below upward. The impulse spreads across the interventricular septum from right to left. According to Sodi-Pallares,[6] it is initially delayed at the boundary between the right septal mass and the left septal mass. This "barrier" is some 2 mm. thick and near the right septal surface.[15] The delay here lasts about 0.02 to 0.04 sec.[14] More recently, Medrano[34] has reported a delay of 0.060 to 0.070 sec. The left septal mass is then activated from right to left, a direction that is reverse from normal; this process takes about 0.02 sec.[6,15] The propagation of this wave is thought to occur through the muscle fibers rather than through the Purkinje system and travels at the rate of about 350 mm. per second.[6,15] Other observations have also indicated that there is a delay within the left septal mass.[21,34] Sodi-Pallares[6] believes that although the activation process moves at this slower rate through the muscular elements, the delay is not enough to account for the marked delay in conduction in the septum as a whole when LBBB is present. With complete LBBB the delay in arrival of the impulse at the left septal surface may be from 0.05 to 0.08 sec.[6,15] The highest portions of the left septal surface show more delay than the middle and lower portions.[6] Once arriving at the left Purkinje network, the impulse activates the left septal surface in a normal sequence and direction without significant delay.[6,15]

Sodi-Pallares[35] has made some recent observations which suggest that there are a few muscular connections between the two septal masses and no delay in conduction at these particular sites, but that there is still a major delay at the "barrier" between the right and left septal masses. Medrano,[34] as already noted, has obtained delays of 60 to 70 msec. between the right and the left Purkinje systems at the middle third of the septum.

QRS interval, thus allowing forces directed away from the effective electrical site of the infarct to become preponderant. As a result, there are terminal S waves in Leads I, aV_L, V_5, and V_6.

Kennamer and Prinzmetal[43] found that transmural infarcts of the left ventricular wall resulted in marked reduction in the R-wave voltage in direct surface leads, whereas patchy or less extensive infarction caused less marked reduction in the R-wave voltage.

Recent studies, already cited, have emphasized the slight influence of the vectorial forces of the free left ventricular wall in LBBB.[41,42] It is not surprising then that Anselmi and associates[42] also found that in the presence of LBBB the pattern recorded over the free wall of the left ventricle had essentially the same configuration (broad R) both before and after transmural necrosis of the free wall.

It is readily apparent that the diagnosis of infarction of the left ventricular free wall (without septal infarction) in the presence of LBBB may be quite difficult or impossible. The appearance of S waves in Leads V_5 or V_6 with inverted T waves in LBBB should suggest the possibility of myocardial infarction. This pattern, however, must be distinguished from displacement of the transition zone pattern to the left In this case the T waves ordinarily are upright. It must also be distinguished from certain cases of uncomplicated LBBB which display terminal S waves in these leads.[49] If S waves are found in Leads aV_L and I, as well as in Leads V_5, V_6, infarction of the high lateral free left ventricular wall should be considered as a possibility.

II. Infarction of the interventricular septum. Infarction of the interventricular septum has been found usually to spare some of the septum. Sodi-Pallares[6,46,47] has distinguished between infarction of the inferior one third and so-called massive infarction of the septum which involves the inferior one half or two thirds, with only the basal segments being spared.

A. MASSIVE INFARCTION OF THE SEPTUM. A lead from within the cavity of the left ventricle in the presence of LBBB complicated by massive infarction of the septum is initiated by a large Q wave (QR or Qr pattern). This Q wave reflects the early negativity of the right ventricular cavity and is detectable in the left ventricular cavity because the necrotic septum acts only as a conductive tissue.[6,46] This Q wave is also recorded in leads which face the epicardial surface of the left ventricle (V_5, V_6, I, aV_L). The depth and duration of this Q wave are thought to be directly proportional to the extent of septal involvement and thus a measure of the upward extension of the infarct in the septum.[6,47]

Complexes of the qrs (QrS) type are encountered in Leads V_3, V_4, (and V_5).[6,47] These patterns are the result of the electrodes being oriented to the high intact portions of the interventricular septum.[6,47] The height of the r wave is proportional to the amount of tissue spared in the interventricular septum.

When the amount of tissue spared in the interventricular septum is small, Leads V_3, V_4 (V_5, V_6) may show a QS pattern which is notched.[47] The r waves which may occur in the right precordial leads in cases of LBBB with septal infarction are thought to be due to activation of the free right ventricular wall,[6] with the early QRS vectors oriented to the right and anteriorly.[49] With massive septal infarction there may be progressive diminution in the height of the r wave from Lead V_1 to Lead V_4.[6]

B. INFARCTION OF THE LOWER ONE THIRD OF THE SEPTUM. In this condition the q wave (qR pattern) present in Leads V_5, V_6 (I, aV_L) is of less magnitude and duration than in massive infarction.[47]

A qRs pattern is found in Leads V_3-V_4 (V_5). The R wave, which is taller than the r wave found in massive septal infarction, indicates less septal involvement.[6,47]

QS patterns are not encountered in this type of septal involvement.[6,47]

III Infarction of the septum plus the free left ventricular wall.

A. MASSIVE INFARCTION OF SEPTUM PLUS FREE WALL. The findings already listed under isolated massive septal infarction are again encountered: (1) Q waves in Leads V_5, V_6 (I, aV_L); (2) qrs (QrS) pattern in Leads V_3-V_4 (V_5) or notched QS; and (3) progressive diminution of the r wave from Lead V_1 to Lead V_4.

Electrodes oriented toward the infarcted lateral free wall of the left ventricle (V_5, V_6) show a pattern similar to that within the

terior, and apical margins. The time for activation of the subendocardial Purkinje fibers at all sites on the left septal surface was *reduced* from the control value of 50 to 60 msec. to 18 to 25 msec. Activation of the muscle fibers beneath the endocardial surface of the left septum was also reduced. Activity in Purkinje fibers preceded activity in adjacent muscle fibers at all points on the left septal surface. These workers concluded that after LBBB, activity enters the left subendocardial Purkinje system simultaneously at multiple points and then spreads to adjacent muscle fibers of the left septal surface.

The initial vector of septal depolarization in LBBB probably corresponds to the activation of the mid-portion of the right septal mass and the bridging of the activation wave from the right septal mass to the left septal mass.[21] It is directed to the left from the lower one third of the right septal surface, inferiorly and somewhat anteriorly, or slightly posteriorly.[21, 22] This produces the initial upstroke in Leads V_5, V_6, and I.[21] The second vector represents the depolarization of the left septal mass in the lower portion of its middle third from the interseptal "barrier" to the lower portion of the left septal surface near the papillary muscle.[21] It is directed from right to left, backward and downward (sometimes upward), and accounts for the major portion of the upstroke (R wave) in Leads V_5, V_6 (I) and the downstroke (S wave) in Leads V_1-V_4.[21] The third vector of septal depolarization is located in the middle and upper third of the left septal mass and is directed from right to left, superiorly, and backward.[21] The latest portion of the left septal mass to become depolarized is the anterior basal portion.[21] The activation process is quite slow as it approaches the endocardium of the left septal surface.[21] This is thought to give rise to the major portion of the slurring and notching (plateau formation) of the R waves in Leads V_5, V_6 (and I) and slurring of the S waves in Leads V_1, V_2.[21] In earlier studies[15] the delay in crossing from the right to the left septal masses was thought to be the principal cause of slurring of the R wave.

The activation of the free left ventricular wall produces the fourth vector, which is directed to the left, posteriorly, and either superiorly or inferiorly, and accounts for the second peak of the R wave in Leads V_5, V_6, and I and the final portions of the S wave in Leads V_1, V_2.[21] There is also evidence that the activation of the free left ventricular wall actually adds little to the QRS complex in LBBB, the major factor responsible for the pattern being the abnormal septal depolarization.[41, 42] Kennamer and Prinzmetal,[40, 42] however, believe that the depolarization of the subepicardial muscle of the free left ventricular wall alone is responsible for the abnormally large epicardial R waves in LBBB.

Left bundle branch block and myocardial infarction

It has been well recognized that the electrocardiographic diagnosis of myocardial infarction in the presence of LBBB is difficult and frequently impossible.[44, 45] This is especially true if the infarct is old or if it does not involve the interventricular septum.

Sodi-Pallares and co-workers[6, 46, 47] have made some interesting observations concerning this problem, and they believe that it is often possible to diagnose myocardial infarction complicated by LBBB, and that in the presence of septal infarction the diagnosis is even facilitated by the occurrence of LBBB. Kennamer and Prinzmetal[42] have also studied the problem experimentally.

A brief review of some of these concepts will be presented as they apply to old (not recent) myocardial infarction.

I. Infarction of the free wall of the left ventricle. With LBBB, infarction of the free left ventricular wall may or may not be evident in the electrocardiogram. The prevailing QRS-T pattern within the cavity of the left ventricle in LBBB is an RS with an inverted T wave.[6, 40, 44, 45]* When there is transmural necrosis of the free left ventricular wall, the vectorial forces of this portion of the free wall are eliminated and an RS pattern (with inverted T wave) may be recorded in Leads V_5 and V_6.[6, 42, 45] The S wave has been explained as a reflection of the cavity potential (RS pattern). Others[43] have invoked the failure of the infarcted portion of the free left ventricular wall to generate potential during the terminal portion of the

*Other patterns encountered in the left ventricular cavity in LBBB have been an R, and in the upper septal area, a qR.[40, 42, 44, 45]

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cavity of the left ventricle (qrs, QrS).[6,47] The r wave is low because only a small zone of the high portion of the interventricular septum is spared.[6] The S wave is thought to be a result of the late septal forces oriented upward, and to outwardly directed forces in the uninvolved free left ventricular wall. If the high lateral portion of the free left ventricular wall is involved, S waves may also occur in Leads I and aV_L. A qR pattern in Leads I and aV_L suggests that the infarction has spared the high lateral area of the free left ventricular wall.[6,47]

B. INFARCTION OF THE LOWER ONE THIRD OF THE SEPTUM PLUS FREE WALL. The septal infarction, as already indicated, produces Q waves in Leads V_5, V_6 (aV_L, I), and a qRs pattern in Leads V_3, V_4. The involvement of the free wall results in S waves in Leads V_5, V_6, and with high lateral involvement, S waves may also occur in Leads I, aV_L (qRs, qRS).

We have confirmed the occurrence of some of these patterns in patients with LBBB and myocardial infarction in an autopsy-controlled study.[50]

Summary

The current concepts of ventricular activation based upon recent studies in the normal heart have been reviewed. These concepts include the activation of the left and right septal surfaces, the septal mass, and the free right and left ventricular walls. The roles of the bundle branches and the Purkinje system are emphasized.

The alterations in ventricular activation that occur as a result of complete left bundle branch block (LBBB) are summarized. The evidence for and against a physiologic "barrier" between the right and left septal masses is presented.

The vector representation of depolarization of the septum and free ventricular walls in the normal heart and in LBBB is briefly summarized.

Some of the newer concepts of ventricular activation in LBBB and myocardial infarction are reviewed.

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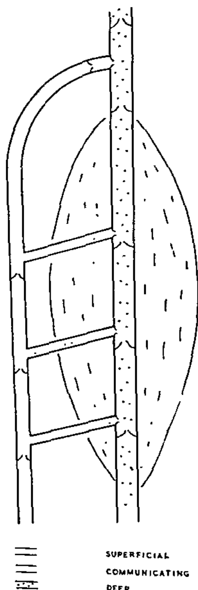


Fig. 1. Diagram of the functional anatomy of the leg veins.

in both the superficial and the deep systems of veins at any level in the leg is the same,[16,17] and close to that of a column of blood extending from the right atrium.[18,23] Under these circumstances it is presumed that all valves are open, and that venous return is by the *vis a tergo* of arterial pressure.

With rhythmic exercise of the leg in the erect posture, measurements of venous pressure reveal a number of features:

During contraction of the muscles the deep vein pressure in the calf rises steeply to a peak, and falls again on relaxation[17,31] (Fig. 4), following the pattern of muscle pressure in the calf (Fig. 3). The superficial venous pressure behaves similarly,[19,21,22] although with a lower peak and higher trough when compared with deep venous pressures at the same level[17,31] (Fig. 4).

During relaxation of the muscles the superficial venous pressure crosses or runs parallel to the deep venous pressure[17,31] (Fig. 4), and it is only at this time that flow from superficial to deep venous systems can take place. Phlebograms have been taken with the subject erect, before and after exercise,[24-27] but it would seem that no attempt has been made to demonstrate directly this presumptive dynamic flow pattern during exercise, by, for instance, cineradiography, or to examine the effects of the contraction of the muscles of the calf on the caliber and course of the communicating veins.

With maintained rhythmic exercise, both the *mean* superficial[17-23,28-30] and the deep[17,31] venous pressures in the calf fall to new levels, but the former pressure always remains the higher (Fig. 5). On the other hand, *passive* rhythmic pumping of the muscles of the calf (Fig. 6), although effecting as great a drop in venous pressure as does active exercise, produces an *identi-*

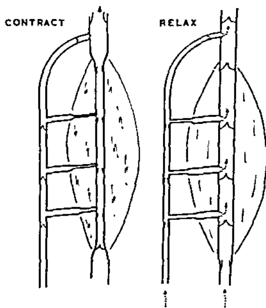


Fig. 2. The concept of the muscle pump.

Functional aspects of the veins of the leg

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A considerable body of literature exists on the anatomy of the veins of the leg, and on the characteristics and distribution of their valves.

From the point of view of over-all function, it is convenient to divide these veins thus (Fig. 1): (a) *deep veins,* within the fascial envelope of the leg, including intermuscular and intramuscular veins; (b) *superficial veins,* in the subcutaneous tissue, notably the internal and external saphenous veins and their tributaries; and (c) *communicating, or perforating, veins,* which join the two former systems. The more important of the latter, functionally and clinically, penetrate the deep fascia along a vertical line behind the medial border of the tibia, joining directly or indirectly the posterior tibial vein to the internal saphenous system.[1-4] Similar veins join the deep and external saphenous systems.[1,2]

The venous valves

All these groups of veins contain valves, which are bicuspid, with frail leaflets thickened at their attachment to the walls of the veins.[4,5]

The highest valve-pair, lying in the external iliac or femoral vein above the saphenofemoral junction, is absent in 20 to 50 per cent of limbs.[6-12]

Some 7 valve-pairs lie in the internal saphenous vein itself,[6] with a constant 2 pairs in the terminal 5 cm.[6,7] The majority lie immediately below the point of entry of tributaries.[5]

The major deep veins are equally liberally supplied with valves, with up to 5 in the femoral vein,[7,10,11] as are the intramuscular veins, with the notable exception of the venous sinuses of the soleus muscle.[3]

The communicating veins possess valves which permit one-way flow from superficial to deep veins[8]; the most constant site is at the point of entry to the deep vein.[1]

The muscle pump

The concept of a muscle pump to assist venous return is an old one. Examination of the anatomic arrangements of the deep veins and their valves suggests a series-parallel system of reciprocating pumps extending up the limb. The input to each pump comes from the deep vein below, and from the corresponding segment of superficial vein through communicating veins. The output is discharged upward into the deep vein pump nearer the heart (Fig. 2).

The motive power for the pumps is provided by contraction of the muscles. On strong contraction of the muscles of the calf, direct[13,14] and indirect[15] measurements have shown pressures of up to 90 mm. Hg,[14,15] with lesser pressures developed in the muscles of the thigh.[14] This aspect of the pump mechanism has, however, apparently been neglected by investigators with more modern techniques.

It is well known that when a subject is erect and completely at rest, the pressure

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ficiency of the pump mechanism in the calf.

It is important to recognize that even the very slight muscular movements which occur during normal quiet standing are sufficient to maintain the superficial venous pressure at a level well below the simple hydrostatic one.[30] The latter pressure evidently obtains only under artificial conditions.

These changes in *pressure* in the veins of the leg are no more than reflections of the changes in the spatial and temporal patterns of venous *flow*. However, the changes in venous pressure themselves might be expected to cause changes in the magnitude of arterial flow. When the subject is in the erect posture, the fall in venous pressure produced by the calf pump increases the arteriovenous pressure difference, and, therefore, the perfusion pressure, in the distal tissues. Thus, it has been demonstrated that in the foot an increase in (skin) blood flow of up to 60 per cent may be produced by passive calf pumping when the subject is in the sitting position.[35] During exercise of the muscles of the calf the additional energy expended in raising the intramuscular pressure not only copes with the manifold increase in venous return,[36] but, by increasing the perfusion pressure, may actually increase the peak arterial blood flow attainable. Conversely, a failure of deep venous pressure to fall on exercise limits distal skin[35] and, probably, muscle arterial flow.

Primary varicose veins—pathogenesis

That varicosities of the superficial veins of the leg are associated with a partial or complete failure of the superficial venous pressure to fall on exercise is well documented.[20-23,28,37-39] These findings confirm those obtained by the use of clinical tourniquet tests,[40] that in subjects with "primary" varicose veins the valves of the superficial system are functionally ineffective. Although the internal saphenous valves are reduced in number when the saphenous vein is varicose,[5,8] it is not certain whether the functional defect occurs primarily in the valve leaflets or as a result of dilatation of the vein at the site of the valve.[4,41] On present evidence the latter seems to be more probable. A slight increase in mean venous pressure can be shown to render a previously competent valve entirely incompetent.[42] The effect of a rise in environmental temperature in increasing the superficial venous pressure on exercise[21 29 30] or tilting[30] is usually explained by the increased flow of blood in

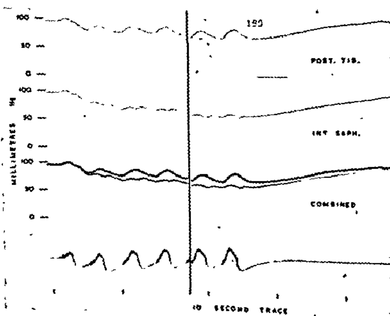


Fig. 5. Pressure measurements as in Fig. 4, but electronically damped.

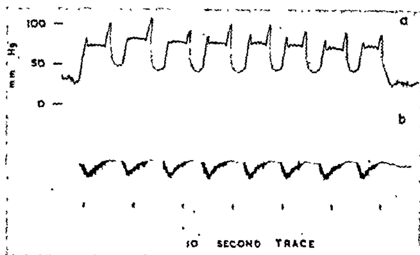


Fig. 3. The effect that rhythmic stepping has on the pressure in the medial head of the gastrocnemius muscle is shown (*a*), with simultaneous electromyograph (*b*).

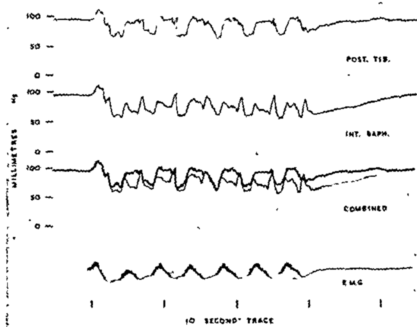


Fig. 4. Simultaneous measurements of pressure during rhythmic stepping, at the same mid-calf level in the posterior tibial (*post. tib.*) and internal saphenous (*int. saph.*) veins, with simultaneous electromyograph (*E.M.G.*). Combined traces are superimposed: the dark trace is the posterior tibial, and the light trace is the internal saphenous.

cal fall in the superficial and deep systems.[21] This suggests that the higher pressure in the deep venous system on exercise is due to the greatly increased muscular venous return.

With static rhythmic exercise the mean pressure in the popliteal vein *does not* decline,[17,32,33] in contrast to that in the posterior tibial vein.[17,31] The absolute level of internal saphenous pressure at the knee on exercise is also higher *than* that at mid-calf level.[31] This is consistent with the lower intramuscular pressures attained *in* the thigh,[13] and emphasizes the great ef-

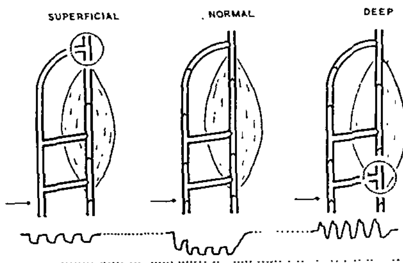


Fig. 7. The anatomic situation (*above*) and the effect on venous pressures at the ankle (*below*) during rhythmic exercise with the leg *normal*, with gross *superficial* valvular incompetence, and with incompetent communicating (*deep*) veins.

ery should be excellent, unless sufficient dilatation of collateral veins occurs to render their valves, in turn, incompetent.[51] The regrettable fact is that long-term follow-up studies of modern surgical treatment are rarely adequate.[52] However, several[52-54] suggest no decline in the proportion of good results with time. Conversely, in a majority of cases of "recurrent" varicose veins the original surgery is inadequate.[50,53,54]

The distinction is of even more significance with respect to the management of very early varicose veins. If there is a widespread defect of the wall of the vein, then sclerosing of these small varices by injection as a stopgap, as is almost universally practiced, is entirely reasonable, and the development of further varices must be accepted as inevitable. If, however, the hypothesis of sequential valvular incompetence is correct, it would seem to be essential at an early stage to attempt to *prevent* progress of the disorder by placing competent valves between the right side of the heart and the skin, i.e., by carrying out at least an adequate ligation in the groin, in addition to cosmetic treatment.[53]

Changes in the skin

The appearance of changes in the skin in relation to varicose veins is associated with failure of the superficial venous pressure to fall on exercise.[20,21,33] This can come about through incompetence of *many* or all of the valves in the superficial system of veins, or, at the other extreme, by incompetence of the valves in *one* communicating vein near the ankle, usually combined with valvular damage in the deep veins (see Fig. 7). The precise consequence of, or association with, the persistently high superficial venous pressure which leads to the skin disorder is still obscure, however.

The first situation is represented by those with gross primary varices, in whom correction of the physiologic defect can be fairly readily achieved, as outlined above.

The second situation commonly comes about from the valvular destruction consequent upon recanalization of a thrombosed vein.[51,55] In these "post-thrombotic" legs there has evidently been both destruction of the valves of the deep veins from a pre-existing deep venous thrombosis,[55,56] and, therefore, failure of the muscle pump, and damage by a similar mechanism of the valves in the communicating veins.[2] The treatment of this state of affairs, from the point of view of the disorder of venous physiology, presents an apparently insoluble problem. Ligation of the femoral or popliteal veins in order to break the column of blood in the deep venous sys-

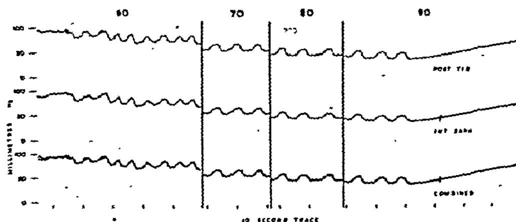


Fig. 6 Posterior tibial (*post tib.*), internal saphenous (*int. saph.*), and combined venous pressure tracings in the relaxed standing posture. The effect of passive rhythmic calf pumping with a cuff inflated to increasing pressures (*above*, millimeters of mercury).

the skin. It could equally represent valvular incompetence associated with venodilatation.

A widely accepted concept is that sequential incompetence of the valves of the internal saphenous vein from above down *precedes* the appearance of varicose veins.[43] As each valve fails, succeeding segments of vein are exposed to progressively greater hydrostatic pressures. Coughing and straining raises the femoral venous pressure to at least 180 mm. Hg,[42] and the transmission of such pressures to the internal saphenous valves can readily be imagined sometimes to ultimately cause their incompetence. On the basis of this hypothesis, a constant corollary of varicose veins would be the functional incompetence or absence of the valve-pair above the saphenofemoral junction, and this seems to be so.[42]

In the case of the external saphenous system, a peak pressure in the popliteal vein of about 130 mm. Hg on contraction of the muscles[17] could be considered to be the damaging factor, although free communication with an incompetent internal saphenous system often accounts for these varices.[44]

The strong familial tendency to varicose veins,[42,43-45] which, incidentally, has rarely[45] been adequately studied from the genetic point of view, may be explained by inborn defects or absence of valves,[4] and such a familial pattern has been shown in living subjects for the valve-pair above the saphenofemoral junction.[42]

There is, however, an alternative hypothesis which would explain all these observations, viz., that the inborn defect is a much more general one of the walls of the veins,[5,50] and that valvular incompetence, although it undoubtedly occurs, is a *result* of the dilatation rather than a cause,[5] and may presumably occur in a *random* rather than sequential manner. The changes in superficial venous pressure in the presence of varices would likewise be considered to be a result rather than a cause, and the varicosities to have developed in response to ordinary rather than extraordinary venous pressures.

Primary varicose veins—treatment

The quibble is more than academic, for present-day treatment of primary varices is based—*post hoc* if not *ante hoc*—on: (a) remedying the *functional defect*, by channeling the blood in the superficial venous system through competent communicating and deep veins; and (b) remedying the *cosmetic defect* by the extensive excision of the superficial varices, or by their injection with sclerosants.

On the basis of either hypothesis, such treatment would be expected to, and does, produce a good immediate cosmetic effect. The importance of the distinction between the hypotheses is that, on the first, the long-term results of adequate initial surg-

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Vascular headache. The headache associated with "vasomotor instability"

The pain associated with changes in caliber of the arteries in and about the cranium has had a good deal of attention, especially since Harold G. Wolff[1] imposed some order on the subject with his excellent book published in 1948. Such a ubiquitous symptom as headache deserves considerable attention.

The pain associated with spontaneously occurring vasomotor reaction in the scalp is usually termed *migraine.* It is this condition that I will consider. I find that I derive a better understanding of any topic if I can examine it with low-power (rather than high-power) lens, so to speak. Accordingly, I would admit to the category of migraine many spontaneously recurring bouts of pain in and about the head, neck, thorax, and abdomen, including such disorders as cluster headache or histaminic cephalgia (Harris's *migraine*),[2] facial neuralgia (hysterical face pain, as Engel[2] has called it); pseudoangina,[3] and abdominal migraine. In these conditions it seems that there is something the matter with local vasomotor regulation, and episodic pain is the main symptom.

Psychological factors. A psychological pattern of some uniformity can be derived in persons suffering these syndromes. Migraine patients are intelligent, tense, striving, orderly, perfectionistic people, inflexible in their attitudes. Their underlying problem is that they have not learned the constructive uses of aggressive feelings. Obstinacy is one of their best defenses. They are unaware of the security of the mind unembarrassed by unconscious rage. In their early life they have somehow been conditioned to depend on others for approval, and they value other opinion more highly than their own. This gaining of approval from others, that is approval other than genuine and relaxed self-approval, is a difficult way of life. It is bound to fail in dealing with people (rather than things). Other persons cannot be expected to deliver emotional supplies with any consistency, undoubtedly the most satisfactory climes for the good life are those that originate from within.

With aggressive feelings converted into brooding or vengeful longing (the migraine sufferer's memory is like that of the elephant!), little wonder that life is punctuated with minor explosions. The attack usually appears in a setting of angry feelings (unconscious) associated with sustained resentment, anxiety, and frustration, in what might be considered as a state of energy depletion. Migraine may be looked upon as a way of life.

It should be noted that there are persons of comparable personality pattern who never have had migraine; the disorder is not that simple. The determinants of human behavior are always multiple. Although there are several factors involved in the production of headache, it can be shown that sociocultural events experienced as noxious precede the appearance of these headaches.

Physiologic factors. Between attacks of migraine, when the subject is considered to be well, the extracranial vessels of the scalp and neck may be varying in tone and diameter. This is not found in people who do not have migraine. The *migraine* attack is accompanied by a state of vasoconstriction followed by one of vasodilatation in and about the cranium. All sorts of neurological signs may appear as aura, most commonly they are in the visual apparatus. These are belived to result because of cerebral vasoconstriction. We now know that local vasodilation may be associated with pain, as the swelling vessel wall impinges upon pain fibers in the adventitia.

Biochemical factors. But there is more to the matter than psychologic and vasomotor reactions. A powerful vasodilator substance "neurokinin," accumulates in the walls of cranial vessels and adjacent perivascular tissues in relation to the migraine attack. This substance lowers the pain threshold and increases capillary permeability.[14]

Therapeutic factors. Since the chronic headache syndrome known as migraine is the result of a complex dynamic interaction between a genetically determined potential and constantly changing psychological, social, and chemical or physical environments, therapy may be approached from a number of directions.

Perhaps the most logical step in treatment might be termed re-education, which cannot be practiced unless it is based on a careful review of the patient's story and the performance of a thorough physical examination. With the confidence gained from them (by patient and physician), the physician is prepared to launch into a simple explanation in nonmedical terms of the nature of the headache, based on the physiologic, biochemical, and psychological principles already enunciated. This may be all that is required to break up a series of vicious headaches. The assurance gained by the patient that he does not have some devastating disease, brain tumor mainly, re-inforced, to be sure, by the care with which the physician has evaluated the problem, may halt the trouble forthwith.

Persons with migraine need some insight into their emotional patterns. Since the migraine patient is almost invariably intelligent, the general physician usually can bring him around to the realization that his overly conscientious attitudes do not constitute a pleasant way of life. Uncovering or insight psychotherapy usually is best left to the competent psychiatrist, well versed in the dynamics of behavior and possessing a proper meld of humility. Sometimes goals need to be limited since there is an irreducible minimum of people who have got to have some headache; it is the best bargain that they can achieve in their rigidly constituted way of life. Erik Erikson[4] has defined such a relationship as that " in which the observer

Annotations

Precision in auscultatory terminology

Two canons of cardiac auscultation are sometimes lost sight of. (1) There are four normal heart sounds (or two, each with two components) due to individual valve closures. (2) The temporal relationships of the heart sounds are strictly dependent upon the cardiac hemodynamics, *no matter where the sounds may be perceived*. Although these considerations are quite clear to the cardiologist, others (especially medical students and house officers) may have difficulty in conceptualizing both normal and abnormal sequences of events because of the common use of loose and redundant terminology.

At clinical rounds and meetings and even in the pages of leading journals, one may note expressions such as "split pulmonic second sound" and "accentuated M_1." These descriptions are doubly inaccurate with regard to canon (1), since each valve closure sound is indivisible (at least to the ear): which are audible in the most unconventional locations normally must preserve the sequence: Mitral-Tricuspid—Aortic-Pulmonic. Moreover, the conventional areas of predilection may be especially faulty under a variety of circumstances, e.g., congenital abnormalities, cardiac displacement, and in the very common instance of pulmonary emphysema.

Terminology should describe events as precisely as possible, if only to avoid perpetuating inaccuracies in the teaching and clinical application of basic concepts. If descriptive terms can also be simple, so much the better. They need not be uniform, although this has advantages, as long as they express correctly what is meant. Accordingly, one might use one of the schemata shown in Table I. The areas where any of these sounds are best heard can be mentioned anatomically, e.g., "left upper sternal border," instead of "pulmonic area."

Table I

Descriptive	*Symbolic*
I. Four normal heart sounds*	
Mitral sound	M
Tricuspid sound	T
Aortic sound	A
Pulmonic sound	P
or II. Two sounds, two components each†	
First sound, first (or mitral) component	1-M (or S_1-M)
First sound, second (or tricuspid) component	1-T (or S_1-T)
Second sound, first (or aortic) component	2-A (or S_2-A)
Second sound, second (or pulmonic) component	2-P (or S_2-P)

*These could also be termed closure sounds, e.g., "mitral closure sound."
†Where paradoxical splitting is a possibility, numbering rather than naming the components would be preferred.

they are neither split nor is there more than one such sound for each valve. Hence, the implications of "M_1" or "P_2" are both false and misleading. Even if one uses a two-sound, two-component schema, asynchrony is the normal situation, and a precise description of any *abnormal* splitting would be required.

Terms such as "pulmonic" or "mitral" and symbols such as "P" and "M," when used to indicate chest surface areas of supposed auscultatory predilection (rather than the valve itself), are at best redundant in terms of canon (2). Heart sounds

A minor polemic. Of some interest, but of considerably less importance because it is not misleading, is the prevalent redundancy "friction rub." The dictionary translates this formulation as "frictional friction" or "rubbing rub." It would be preferable to use "rub" or "friction sound", e.g., "pericardial rub."

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toms, and the magnitude of the shunt. The first consideration is beyond the scope of this discussion except to state that any single operation by open-heart techniques is inherently hazardous, however safe the procedure may seem to be on a statistical basis. The presence or absence of symptoms is often a question to which the answer is clouded by variations in interviewing techniques and in the patient's attitude toward the problem. Easy fatigue, which is, in our experience, one of the most common symptoms, is particularly hard to assess for obvious reasons. Of the three considerations listed, the magnitude of left-to-right shunting is the only one susceptible to numerical measurement. Such measurements represent approximations and by themselves provide a slender basis for selection. As early as 1953, Gross[2] recommended closure in children in whom the ratio of right ventricular output to left ventricular output was 1.5 to 1 or more. Such a value is little greater than that of 1.25 to 1, the ratio suggested by Michaels and Parkin[3] as that below which clinical detection of the defect could not be reliably achieved. If such mild degrees of shunting are accepted as worthy of surgical intervention, it is easy to see why clinical diagnosis alone is viewed as sufficient basis for operation in some centers.

Measurement of exercise tolerance under controlled conditions is worthy of attention in this respect. Such procedures seek to bring out latent deficits of physical performance by measurement of heart rate, ventilation, and various respiratory gas concentrations with appropriate calculations. Such tests are not only safe and have a high degree of acceptance by the patients, but provide the physician with information obtained during a much greater stress than can be achieved by supine exercise during catheterization of the right side of the heart. Jonsson, Linderholm and Pinardi[4] studied 22 patients on a bicycle ergometer at varying work loads. Twenty of these patients had systolic pulmonary arterial pressures of 33 mm Hg or less. The scores indicated that defective performance was related to advancing age but not to the magnitude of the left-to-right shunt. In our own laboratory, employing a treadmill exercise at 1.7 m.p.h. and a 10 per cent grade, a study of 6 comparable patients revealed normal tests in 3, aged 19, 19, and 24 years, mildly abnormal tests in 2, aged 23 and 34 years, and a markedly abnormal test in 1, aged 50 years. The scores of such tests are, of course, adjusted for age. No correlation with the degree of left-to-right shunting as estimated from analysis of blood oxygen concentrations at the time of catheterization of the right side of the heart could be obtained. It would appear, therefore, that exercise tolerance as measured in these two studies is limited by factors not accounted for in measurements of pressure and flow. One suggestion of Jonsson and his co-workers was that this may reflect defective output of the left ventricle. Such an explanation would usually be subject to confirmation or rejection by study of the cardiac output achieved during a comparable degree of exercise; however, the presence and location of the shunt pose difficulties to such an approach using the Fick principle and indicator-dilution techniques. Nevertheless, the suggestion is reasonable, and it seems to us that a definite loss of exercise tolerance is a factor of value in reaching a decision to operate in the face of equivocal symptoms and normal pulmonary arterial pressure. Furthermore, the addition of such a test to total evaluation of the patient makes it less important to establish arbitrary criteria based on the magnitude of left-to-right shunting.

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Drug-induced malformations in the fetus

During the past few months a remarkable volume of information has accumulated, mainly in Europe, concerning serious fetal malformations which result from the taking of a drug by mothers during pregnancy. This drug is thalidomide or a-phthalimidoglutarimide, an apparently innocuous sedative which was reputed to have no known toxic dose. The proprietary names are Distaval (Great Britain), Contergan (West Germany), and Softenon (Switzerland.) Other drugs with a glutarimide nucleus are known, but there has been no evidence to incriminate them.

Initial reports of an apparent association between the taking of this drug by pregnant mothers and the subsequent birth of malformed babies came from McBride,[1] in Australia, and Lenz,[2] Pfeiffer,[3] and Wiedemann[4] in Germany. Because of absent or inadequate records and the fallibility of human

who has learned to observe himself teaches the observed to become self-observant."

The treatment of the symptoms is to try to abort the attack *early* in its course. Drugs taken at the very earliest manifestations of an attack may achieve this. Sometimes, aspirin may serve this function Persons free of cardiovascular disease may take the vasoconstrictor drug, ergotamine tartrate, by one of several routes; by inhalation, by mouth, sublingually, rectally, or parenterally.

If the attack is established, there is little to be done beside attempt to promote rest in a quiet, darkened room. Partial compression, with the thumb, of the carotid system on the same side as the head pain is effective in halting unilateral headache for as long as the compression is maintained; this may allow the patient to get to sleep. The patient usually awakes free of headache. An icebag over the carotid vessels may serve as well to reduce the thrust of the pulse (throbbing headache). The injection of a sedative drug may become necessary to promote sleep.

Prophylactic treatment of the attacks of migraine may be useful, particularly of cluster headache, which is the type that recurs frequently. Ergotamine tartrate, usually 2, and occasionally 3, tablets of 1 mg each per day, taken over a period of a week or two, may break up a series of closely recurring attacks. Because this drug is not well absorbed orally, it may be used in prophylactic symptomatic treatment by injection, sublingually, rectally, or by aerosol insufflation. The main untoward effect of ergotamine tartrate is its propensity to induce nausea and vomiting, it is contraindicated in vascular disease, hypertension, pregnancy, kidney and liver disease, sepsis, and cachexia.

If patients with frequent migraine attacks do not tolerate or respond to the usual symptomatic use of ergotamine tartrate, a course of methysergide maleate may be tried This substance is an antiseotonin agent. The average daily dose is 4 to 8 mg. daily for a 3-week trial. Occlusive vascular disorder has resulted rarely with the use of methysergide meleate.

Sedative, analgesic, and "tranquilizing" drugs have limited uses in migraine. An occasional stubborn case may be transiently benefited with corticosteroids. Corticotropin in doses of 20 to 30 units has been known to abort weekly or monthly attacks of migraine. The corticosteroids should almost never be used in migraine.

A variety of untoward circumstances are at work to result in an attack of migraine; these include personality problems, altered vasomotor tone, and the local production of a noxious agent or agents capable of lowering the pain threshold. The sheet anchor of treatment is a conscientious elicitation of history and the performance of a thorough-going physical examination. These simple measures are more often neglected than not. Their proper performance is the basis for a therpaeutic program; indeed, they are the first indispensable step in any treatment

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Exercise performance and cardiac surgery in uncomplicated atrial septal defect

An atrial septal defect in which the only hemodynamic manifestation is left-to-right shunting may be tolerated without symptoms and is compatible with excellent life expectancy.[1] These facts may well cause the conservative physician to hesitate in recommending surgical closure. On the assumption that catheterization of the right side of the heart has been performed and has demonstrated the magnitude of shunting and the absence of pulmonary hypertension, there is little to be gained from further hemodynamic study. A search of the literature does not provide a precise basis for assessment of long-term risks, since available studies do not provide data which justify the assignment of higher risks to individual patients within this group of uncomplicated cases. In effect, the decision is likely to be based on the quality of surgical treatment available, the presence or absence of symp-

Book reviews

DIAGNOSIS AND MANAGEMENT OF PAIN. By Bernard E. Finneson, M.D., F.A.C.S., Neurosurgeon, The Episcopal Hospital, Philadelphia. Philadelphia, 1962, W. B. Saunders Company, 261 pages. Price $8.50.

This book on pain is a good and practical one. It is written from the point of view of the neurosurgeon. It includes many simple illustrations concerned with diagnosis, localization, areas of referral, and management.

Pain is one of the most common and most annoying symptoms of disease in man. It concerns physicians in every field of medicine. Although this book is not specifically intended for cardiologists, it should interest them greatly, for it is they who are concerned at all times with pain in diagnosis and management. Chest pain has many sources of origin other than the heart and blood vessels. It is the extracardiac types of pain which offer so much difficulty, and which this book is about. Even though one may not agree entirely with all ideas presented, this is a useful, simple, and well-illustrated book.

HEALTH AND FITNESS IN THE MODERN WORLD. A Collection of Papers Presented at the Institute of Normal Human Anatomy, and the Ministry of Foreign Affairs, Rome, Italy. Published by The Athletic Institute in cooperation with The American College of Sports Medicine, 392 pages. Price $4.50.

During the Olympic Games in Rome, in 1960, experts in the field of sports medicine, physical education and fitness congregated to exchange their ideas and experiences on the status and concepts of "fitness" in their home countries. Thirty-eight participants from 16 Western and Eastern nations set the stage for scientific discussions by presenting formal papers. These papers were collected in this book as a documentation of world-wide research activities concerned with providing some of the needed facts for the understanding and knowledge of good health and general "physical fitness" In the present days of awakening concern about man's waning resistance to the strain and stress of daily life and to emergencies—as a consequence of all the technological progress making human life too comfortable—such understanding becomes essential for organizing adequate countermeasures against the process of decay. Thus, this book should be of special interest to general physicians and to specialists in several medical fields who are not only concerned with acutely effective therapeutic procedures but who are also thinking in terms of preventive and rehabilitative measures of health.

The book does not impress as an entity. With the involvement of so many contributors—most of them discussing only small sections of their research interests—a well-rounded, informative brochure was not to be expected. However, the material presented and discussed in Rome was so diversified that one area or the other should catch the potential reader's interest, with favorable or antagonistic reactions. Psychological and educational aspects of physical activities and sports were as expertly covered as were neurophysiologic, cardiorespiratory, and metabolic aspects, in addition to problems of genetics, performance rhythms in sports, or overtraining. Even philosophic considerations of amateurism and sportsmanship in modern sports have come to word.

There is a strongly growing trend in the United States to apply tests of functional and metabolic adaptive capacity—tests which have become well established for the assessment of "fitness" in the "normal"—on a variety of patients for a variety of reasons, e.g., for diagnostic purposes, for the evaluation of the effects of certain treatments, for establishing the failure or success of rehabilitation techniques, etc. Everyone who wishes to obtain basic information on "normal" responses to physical work and on the limitations which might separate the poor from the fair, or the excellent from the superior performer, should attempt to read carefully some contributions of authors from Austria, Bulgaria, Finland, France, Germany, Italy, and the United States—even if the reading might become severed by language barriers. Undoubtedly, this book has great assets in its favor: it stimulates the thinking about present-day health problems of the "healthy," evokes here and there justifiable criticism and the urge to collect research facts for a scientific re-battle, and it opens up a few avenues for further research on interesting problems in human biology.

LA TRASPOSIZIONE DEI GROSSI VASI. STUDIO RADIOLOGICO (The Transposition of the Great Vessels). By F. Fossati, F. Barbaccia, and G. Pompili. Turin, 1961, Minerva Medica, 213 pages, 103 illustrations. Price: 6,500 lire ($11.).

This Italian monograph contains a complete review of the problem of transposition of the great vessels. Embryologic and anatomic studies, the clinical picture, and the electrocardiograms and phonocardiograms of the cases are discussed in detail and illustrated by excellent schemes and original graphs. Catheterization data are briefly reported.

In the second half of the book, the data obtained in the roentgenologic study of the clinical cases with and without contrast media are discussed in detail and illustrated by original documents of high quality. The data supplied by roentgenkymography, aortography, and coronary angiography are then presented. In addition, the differential diagnosis and the treatment of these cases are discussed in detail. Six personal cases are described at the end of

memory it was not possible to prove this relationship in many cases. The more detailed the interrogation and scrutiny, however, the closer the correlation. This association has now been demonstrated in the United Kingdom, West and East Germany, Sweden, Belgium, Switzerland, Australia, Canada, Lebanon, and elsewhere. Businessmen visiting West Germany have taken this drug home to their wives, who have later had malformed offspring. Similar malformations have now been produced in animals.[5] The question now is how this drug acts, and not whether it acts.

The most obvious abnormalities have been those of the limbs, with hypoplasia or aplasia of the long bones resulting in various forms of phocomelia or amelia. These were usually bilaterally symmetrical, but not always so. Cardiac malformations, such as septal defects, common truncus, right-sided aorta, etc., also occurred. Almost every system except the nervous system has been affected, and other malformations included: atresia of esophagus, duodenum, jejunum or anus, undue mobility of cecum with absent appendix, absent gall bladder, absent auricles, capillary nevus of nose and upper lip; partial defects of limb girdles; anomalies of kidneys—hypoplasia or hydronephrosis.

In the present stage of our knowledge it is a reasonable suggestion that this drug disturbs the growth of tissues developing from mesenchyme. Thus, outgrowths of mesenchyme form the auricles, cecum and appendix, limb buds and ventricula septa, and these have all been described as defective. It is to be hoped that the considerable amount of research in animals which has been initiated will throw some much needed light on the cause of congenital defects generally, and that some benefit may accrue to balance the widespread human suffering that has resulted.

There is evidence that, since 1959, about 3,000 affected babies have been born in West Germany, where thalidomide could be bought without a prescription. In Great Britain, where a doctor's prescription was necessary, the incidence has been far less, and has varied from area to area, depending on local habits of prescribing. Finally, in the United States, the drug was not available, since the necessary probationary period of 2 years laid down by the Food and Drug Administration was not yet up, and I believe that there have been no cases apart from a few in which the drug was taken privately into the country. The rate of introduction of new medicinal substances is increasing. Over 200 new drugs and 800 proprietary medicines have been introduced in Great Britain in the past 3 years. It is essential, therefore, that the most stringent precautions be taken, both by means of the laws of the country and by the pharmaceutical firms, to avoid another disaster. New drugs must be thoroughly tested, not simply on adult animals but on several species of pregnant animals, so that they act during the phase of organogenesis in the fetus. Fetal-developing tissues must be metabolically or enzymatically different from mature adult tissues. This should have been evident from the results of infection by the rubella virus, which, in general, causes little upset to the adult but serious malformations in the fetus.

This experience stresses the need for "early pregnancy care," advocated by Russell,[6] for this is a time when a significant proportion of pregnancies go wrong. Doctors should be advised to exercise care in the prescribing of drugs at this time. According to Taussig,[7] the danger period seems to be about the third to sixth weeks, although cases have been described which may have resulted from the mother's taking the drug as early as the second week. Indeed, serious malformations may occur even before the mother realizes that she is pregnant. It is important, therefore, to start keeping records as soon as the first menstrual period is missed, while details of recent events are still fresh in the memory.

Those undertaking research into the causes of malformations must appreciate the futility of retrospective studies which rely on the human memory. Thus, although these malformations started to appear in Germany in 1959, it has taken the medical profession until the end of 1961 to note this association. There are few prospective researches, such as those by McDonald,[8] and there would seem to be a need for further studies like this since there may be other drugs with a teratogenic effect in use at present.

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Not all the physical mechanisms of production of cardiac sounds in health and disease are discussed, but the basic outline is present, with only moderate sacrifice of detail. This latest edition testifies to considerable effort on the part of the authors to justify another edition of a book by incorporation of new or clarified explanations.

The major defect in the book is the failure of the authors to reassess the section on auscultation of the lungs. The description of râles in the chest is confusing. The authors present diagrammatically a method for classification of these râles, but some of the descriptive subdivisions of râles are discussed in the text as though they were separate entities without distinct relationship to the diagrammatic presentation. In addition, many synonymous terms are used to describe a sound (musical râle, dry râle, rhonchus). The words "sonorous" and "sibilant" have assumed meanings of "low pitched" and "high pitched," respectively, as expropriated by physicians. The authors rationalize this vague and confusing presentation by the attitude that each student will devise his own system of naming râles. This does not seem to be a wholly reasonable assumption. Noises within the chest are identical for a given condition but are described variously by individuals because there has been no clear recommendation of a system. The terminology in this section has been preserved since the days of Laennec. Changes in his terminology and classification of râles should be made and accepted, just as his original stethoscope has been radically altered but still is of historical interest in medicine today.

Except for the section on auscultation of the chest, the sixth edition of *Physical Diagnosis* (now coauthored by Dr. Delp and Dr. Major) is a reasonable adjuvant for teaching physical diagnosis.

Herzschall-Fibel. Einführung in die Mechanokardiographie (A Primer of Phonocardiography). By Prof. Dr. med. K. Holldack, Berlin, Ärztlicher Direktor des Stadt. Krankenhause; and Dr. med. D. Wolf, Heidelberg, Universitäts-Kinderklinik. Second edition, Stuttgart, 1962, Georg Thieme Verlag, 116 pages, 72 figures. Price: DM 16.80.

In the foreword to this book, Professor Bamberger, Director of the Pediatric Department of the University Hospital in Heidelberg, home of Dr. Wolf, emphasizes that graphic registration of heart sounds and murmurs as well as pulse curves can furnish exact and important information which is inaccessible to the senses alone. The first edition of the book in 1960, in addition to summarizing the long experience of Dr. Holldack in this realm, also included some of his unpublished work on the interpretation of the venous pulse done at the City Hospital of Berlin-Neukolln. This second edition includes the accomplishments of the last two years, contains more illustrations, and treats extrasounds and accidental murmurs in greater detail. It describes, first, the registration and normal variants of the phonocardiogram, sphygmograms of the carotid and iliac arteries and the aorta, venous and hepatic sphygmograms, ventricular sphygmogram (apex beat), and esophageal cardiogram, and then continues with a description of the modifications of these curves seen in different types of congenital and acquired cardiac disease. These findings are summarized very clearly in the form of tables and schematic diagrams. The illustrations include tracings of phonocardiograms in at least three bands, registered together with the electrocardiogram and pulse curves. This condensation of the larger textbook of phonocardiography by the same authors is well suited for the student or clinician with cardiological interests.

Congenital Cardiac Disease: A Review of 357 Cases Studied Pathologically. By Robert S. Fontana, M.D., M.S.(Med.), Consultant, Section of Medicine, Mayo Clinic, and Instructor in Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.; and Jesse E. Edwards, M.D., Director of Laboratories, Charles T. Miller Hospital, St. Paul, Minn. Philadelphia, 1962, W. B. Saunders Company, 291 pages. Price $10.

This volume is a highly specialized, excellent statistical presentation of incidence, distribution according to sex, and longevity of 28 different congenital heart anomalies and 19 combinations of these anomalies. Statistics on two complications, endocarditis and cerebral abscess, are also presented. The data are based on the authors' series of 357 autopsied cases, as well as the data of many well-known authors. The major portion of the book is a systematic presentation of each anomaly and combination. Each presentation is composed of three sections. The first two sections are statistics derived from the authors' series and from the data of other workers. The emphasis is on the age of the patient at the time of death, the cause of death, and the distribution according to sex. The combined data are evaluated as though they were derived, for the most part, from a single series and are presented in the third section. Realizing the shortcomings of this approach, the authors believe that their findings represent statistical trends which probably fall short of actual statistics, but which are more representative than data from any one collection of pathologic material. In addition to the statistics on longevity presented with each pathologic entity, the study of length of survival is again presented in a separate section. The authors' series is divided into 27 different age groups and is designed to guide the clinician in differential diagnosis on the basis of age. Although this approach has obvious advantages, it is to be considered as strictly adjuvant to carefu[l] clinical evaluation of the individual patient. I[n] order to give a clearer picture of the natur[al] history of each anomaly, the authors have [ex]cluded from their series the cases of patients'

the book, with detailed protocols and reports of catheterization, as well as of other laboratory data. The bibliography includes 309 items.

The quality of presentation and the editorial aspects of this book are first class. It is recommended to cardiologists and roentgenologists.

HANDBOOK OF PHYSIOLOGY (Section 2, Circulation, Volume I). Section editor, W. F. Hamilton. Executive editor, Philip Dow. Washington, D. C., 1962, American Physiological Society, 758 pages. Price $24.

This is Volume I of Section 2 on the circulation, part of a new series of volumes to constitute a *Handbook of Physiology*. Experts in the field have written the respective chapters concerned with research on the circulation: blood volume, physical equilibria of the heart and blood vessels, rheology of blood, electrocardiography, control of function of the heart, circulation time, heart sound, and other aspects of the circulation.

This is a good volume, but, unfortunately, the chapters are too brief. The authors have been highly selective in quoting from the literature, and no chapter is adequate nor is the literature reviewed sufficiently. The subjects are presented primarily from the author's own point of view. The reader must bear this in mind for it is certain that these chapters will be quoted extensively in the future. Even though a complete presentation is impossible, this volume will find itself among the many complete volumes of the *Handbook*, and perhaps because of this it will give the impression of a thorough presentation of the subject; this will be found to be untrue.

The discussions do not and cannot include a thorough review of the problems as related to pathologic states. Nevertheless, if the lack of completeness and the more or less limited points of view in some instances are kept in mind, this volume is a good one and will be useful to students, physiologists, researchers, teachers, and physicians. The two editors have performed a good service in view of the restrictions in pages available for each chapter. This is a useful contribution.

DIFFERENTIALDIAGNOSE DER HERZSTROMKURVE (Differential Diagnosis of the Electrocardiogram). By Priv. Doz. Dr. Gernot Friese, Medizinische Universitätsklinik, Heidelberg. Berlin, 1961, Springer Verlag, 182 pages, 169 figures. Price: DM 29.80.

The author has been director of the electrocardiographic laboratory of the University Hospital in Heidelberg for more than ten years, and has incorporated into this book some of the contents of his lectures on electrocardiography to staff members of this Hospital. K. Matthes, Director of the Department of Medicine of this Hospital, emphasizes in the foreword to this book that because of increasing specialization the person making an electrocardiographic interpretation often has no chance to make a thorough clinical study of the patient, and that therefore the correlation between electrocardiographic and clinical findings must be made by the clinician. The purpose of this book is to make such a correlation easier. It presupposes familiarity with the basic principles of electrocardiography and, therefore, rather than supplant existing textbooks, it supplements them. However, to save the reader the trouble of repeated reference to a textbook, the most important electrocardiographic patterns are described in small print, and these descriptions are referred to by page number throughout the text and in the alphabetical index. The legends to the numerous illustrations contain a description of the corresponding electrocardiographic and clinical findings, and the illustrations can be used for practice in the application of the diagnostic rules developed in the text. After introductory remarks are made on the leads necessary in different clinical conditions and the sequence of electrocardiographic analysis, the clinical conditions which may be responsible for certain electrocardiographic patterns are discussed. Among these are axis deviation, P-wave patterns, changes of P-R and QRS duration, S-T displacement, T-wave patterns, Q-T duration, and the U wave, as well as artifacts. Finally, the differential diagnosis of bradycardia, tachycardia, and the arrhythmias is discussed. The short bibliography lists textbooks and some of the most important recent papers. Because of its clear and systematic arrangement the book will be very useful for everyone who must evaluate electrocardiograms or electrocardiographic findings from a clinical point of view. The illustrations contain many unusual and interesting cases even for the advanced cardiologist.

PHYSICAL DIAGNOSIS. By Ralph H. Major, M.D., Professor of Medicine and of the History of Medicine, University of Kansas; and Mahlon H. Delp, M.D., Professor of Medicine, University of Kansas. Philadelphia, 1962, W. B. Saunders Company, 355 pages. Price $7.50.

An introductory textbook to physical diagnosis in medicine cannot hope to represent a complete document. If all the known physical signs were related to their respective physical causes, a very lengthy dissertation would result and would defeat the purpose of an introductory text. Dr. Major recognized this principle in the introduction to his first edition of *Physical Diagnosis*. The sixth edition of the book adheres to this precept, with the exception one brief but distracting discussion of thyroid physiology. The material is artificially inserted into the otherwise unchanged text of the preceding edition; it is recognized readily because of the interrupted presentation of eye signs in thyroid disease and deviation from the intention to avoid complex presentations of physiology. The fundamentals of cardiac auscultation have been extensively revised within the limitations just described.

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Acknowledgment to reviewers

The Editors wish to express their thanks and appreciation to the following who have aided in the review of manuscripts during the past year:

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have undergone cardiac surgical procedures since July 1, 1954. No pathologic descriptions are included in the text.

The authors believe that every major survey of statistics on cardiac anomalies is affected to some extent by various factors of selection. Nevertheless, the data compiled in this volume probably approximate true statistics more closely than do those of any work available at the present time. It is an authoritative presentation of our current knowledge of incidence, distribution according to sex, and longevity of cardiac anomalies and is, therefore, of distinct practical value to the clinician, the pathologist, and the teacher.

Announcements

THE SCIENTIFIC SESSIONS of THE PHLEBOLOGY SOCIETY OF AMERICA will be held in the afternoon of Saturday, Nov. 10, 1962, at the New Hotel Americana, New York City. The subject of the Sessions will be "Peripheral Vascular Diseases."

The registration fee for nonmembers will be $5.

The main program has been arranged, but more papers are invited. Send correspondence to H. I. Biegeleisen, M.D., Executive Director, 135 East 58th St., New York, 22, New York.

Richard H. Orr, M.D., Director, has announced that the headquarters of the INSTITUTE FOR ADVANCEMENT OF MEDICAL COMMUNICATION has been moved to 9650 Wisconsin Avenue, Bethesda 14, Maryland.

The Institute will continue to maintain offices at 30 East 68th Street, New York 21, New York, and at 1028 Connecticut Avenue, N.W., Washington 6, D.C.

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to the most effective and safe use of roentgen rays by pediatric cardiologists.

In order to supply information pertinent to these problems, our group in Pediatric Cardiology has collaborated with the Department of Radiology* in a study of radiation exposure in children with heart disease.[8,9] As we began our investigation 3 years ago, it seemed paradoxical that, in contrast to the large literature available for techniques in adults, we were unable to find dosimetry studies for the routine and specialized diagnostic procedures performed in children. Since the report of Hills and Stanford[10] in 1950, the cardiology literature has remained free of similar extensive studies which included the exposure with chest films, screening with barium swallow, fluoroscopy during cardiac catheterization, and angiocardiography. Hills and Stanford found a total skin exposure of 136 r for an adult patient requiring all of these procedures. Ritvo and coworkers[11] reported, in 1957, a skin dose exposure of 60 r for a 5-minute fluoroscopic exposure during cardiac catheterization. These values are far in excess of exposures involved with currently available image intensifiers. Data on exposure is now becoming available for new techniques, such as image amplification with closed-circuit television employing a television tape recorder.[12] Such equipment, although reducing radiation exposure markedly, involves a prohibitive expense for most groups at the present time. Since the general consensus stresses *minimal radiation dose*, it is apropos that we also consider relative exposures with the various techniques currently in use.

Conventional fluoroscopy. Although routine fluoroscopy is a valuable diagnostic aid in certain cardiac conditions, e.g., corrected transposition of the great vessels, the information gained in addition to that obtained by regular chest films is relatively small in most common cardiac conditions. Wood and co-workers[13] have stressed that an accurate diagnosis of the nature and severity of the great majority of cases of congenital heart disease can be made by a proper bedside examination supported by inspection of the electrocardiogram and x-ray films. Recently, this has been further emphasized by Castle and Craige[14] in their discussion of auscultation of the heart in infants and children. The basic radiologic study should be films, which give considerable information about the cardiac chambers and pulmonary circulation. If sufficient information is not afforded by films, then fluoroscopy may be indicated as an adjunct.

The National Committee on Radiation Protection[15] recommends an output of not more than 10 r per minute for standard fluoroscopes; yet conventional fluoroscopy in children usually can be carried out with less than 5 r per minute. However, marked variation in the radiation output of standard fluoroscopes has been demonstrated by Sonnenblick and co-workers[16] (up to 72 r per minute). Outputs up to 37.5 r per minute were documented by Zavon and Valaer[17] for fluoroscopes used by pediatricians in their office practice. Consequently, the American Academy of Pediatrics advises against the installation and use of fluoroscopes in the offices of pediatricians.[18] Parenthetically, one would have to obtain approximately 333 routine chest films (0.009 r per exposure) to receive the exposure incurred during 1 minute of conventional fluoroscopy at 3.0 r per minute

When fluoroscopy is necessary, a ten-to-fiftyfold reduction in exposure can be obtained by substituting the image amplifier for the regular fluoroscope. With image amplification, studies can be conducted with a direct-beam skin dose exposure of less than 0.2 r per minute.

Cardiac catheterization. The average duration of image-intensifier visualization in 51 children in our cardiac catheterization laboratory was 7 minutes.[8,9] If a conventional fluoroscope with an output of 10 r per minute (the maximum output recommended by the National Committee on Radiation Exposure) had been used, this would have resulted in a direct-beam exposure of 70 r—a dose in the range of that used in the past for x-ray therapy of an enlarged thymus (50 to 100 r). In contrast, image amplification for 7 minutes gave a skin dose of less than 1.4 r.

Angiocardiography. When cardiac evaluation requires contrast studies, either

*Dr. M. Paul Capp, Dr. George J. Baylin, Dr. Joseph K. Isley, and Mr. Aaron P. Sanders.

Editorial

Radiation exposure in children with heart disease

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During recent years, advances in the medical use of ionizing radiation have proceeded at such a rate that most physicians now are directly or indirectly involved in the practice of "nuclear medicine." With the increasing need of ionizing radiation for an accurate diagnosis of many diseases, there has been increased awareness of the possible dangers of diagnostic irradiation to the child or to future generations. Geneticists, biologists, physicists, radiologists, and pathologists are rapidly amassing data concerning the biologic effects of ionizing radiation. On the other hand, the inherent nature of this type of information probably accounts for its lack of transmission with sufficient rapidity to clinicians who have the total responsibility for the care of patients. Since children with heart disease are especially subject to multiple studies involving radiographic techniques, a thorough knowledge of radiation exposure is necessary for all physicians caring for such patients.

Muller has demonstrated that irradiation to the gonad itself is the determining factor in the production of mutations, and he discusses eloquently the damage to posterity caused by irradiation of the gonads.[1] Recently, Schull[2] has presented a geneticist's viewpoint of the radiation hazard, and Webster,[3] the viewpoint of the physicist. These authors admirably discuss the difficulties of transferring to mankind the data obtained in the fruit fly and mouse. However, Robinow and Silverman,[4] in an excellent review of the radiation hazards in the field of pediatrics, aptly state: "There are still gaps in our knowledge of the effects of radiation. Not all controversy will be resolved in the near future. But the burden of proof is on those who scoff at the dangers. The medical profession can draw only one reasonable conclusion as a guide to action: Even medically indicated radiation is potentially harmful. While we are awaiting to find out exactly how much radiation is how bad, let us do our share in reducing avoidable exposure to a minimum."

We cannot overlook the goal stressed by Caffey[5] of a *minimal radiation dose* per examination (consistent with optimal care) rather than the *greatest tolerance dose*. Currently, increased attention to this aspect of pediatrics is being directed specifically to cardiac patients. At the Annual Meeting of the Academy of Pediatrics in Chicago in October, 1960, in the course of the Round Table on Pediatric Cardiology, the value of *x-ray films* was stressed, whereas the use of conventional fluoroscopy was strongly deemphasized.[6] In the 1961 Annual Report of the Section of Cardiology of the American Academy of Pediatrics,[7] the first of future plans included working with the Committee on Radiology in Children as

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2. Existing conventional fluoroscopes should be replaced by image intensifiers as soon as possible, especially in cardiac clinics and cardiac catheterization laboratories for children.

3. Until such time as they can be replaced by image intensifiers, conventional fluoroscopes should be monitored closely to insure the use of minimum radiation outputs consistent with adequate visualization.

4. Each physician should ask the following question before recommending a specific radiologic study, "Can anything further be learned by fluoroscopy, angiocardiography, etc., that is not evident clinically?"

I should like to thank Dr Jerome S Harris, Chairman, Department of Pediatrics, and members of the Department of Radiology for their advice, suggestions, and generous contribution of time for discussion concerning this aspect of pediatric care.

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biplane angiocardiography or cine techniques utilizing an image intensifier may be used. Opinions vary as to the preference of one procedure over the other; however, a comparison of skin exposures is worthy of note. In our laboratory the average cine time (including single and multiple injections) at cardiac catheterization has been 18 seconds per patient. Such a cine study results in a skin dose exposure of 1.0 r, utilizing one of the newer image intensifiers. With uniplane conventional angiocardiography (28 exposures) the total skin dose was 3.4 r. Usually, biplane study is employed, and this results in an additional 9 r to the lateral chest.

These exposures are specific for the x-ray machines studied, and with the newer biplane angiocardiographic equipment available, lower exposures can be obtained. It is now possible to record contrast studies by means of video tape (or kinescope),[12] which technique results in markedly reduced exposures (<0.05 r for 18 seconds).[9]

Radioisotopes. The value of radioisotopes in the study of the circulatory system is now well established. Clinically, this method has been used for the study of cardiac output,[19] intracardiac and pulmonary blood volumes,[20] pericardial effusion,[21] and cardiac shunts.[22,23] Radiation exposure from conventional radiographic studies involves essentially gamma-ray exposure to a localized area of the body, whereas the exposure from intravenously administered radioisotopes usually involves beta- and gamma-ray exposure to the entire body. I^{131} albumin, Diodrast, and Hippuran, which are commonly used in cardiovascular studies, are distributed throughout the body through the circulation. The exposure from the use of such radioiodinated compounds can be approximated from standard formulas.*[24] Although such formulas permit an estimation of total body irradiation, it must be emphasized that these doses as yet cannot be considered to be totally accurate because of the nature of distribution of the isotope in the body. If one requires such information in specific instances, collaboration with the radiologist and radiation physicist is necessary.

If radioactive Hippuran is used, it is rapidly excreted by the kidneys, so that the effective half life in the body is less than 1 hour, even with poor renal function. Precautionary measures include administration of iodine (to block the uptake of I^{131} by the thyroid gland) and adequate hydration to insure early voiding (to minimize pelvic irradiation). With these measures, when 15 microcuries are injected into a child who weighs 40 kilograms, the whole body beta dose approximates 0.0002 rads (radiation absorbed dose), and the gamma dose is 0.00013 r (roentgens). In view of the concern over the use of radioisotopes in children, it is interesting that the gonad exposure from the use of such isotopes (in the dosage mentioned) is significantly less than the gonad exposure from routine chest films[25] and fluoroscopy. Although such calculations may appear to be mere scientific embellishments by the clinician who requires the diagnostic use of ionizing radiation, it is primarily on this basis that judgments can be made concerning the use (and dosage) of radioisotopes in children in the future. Presently, the consensus is that radioisotopes should be used in children only for situations in which information cannot be gained by other methods. It is hoped that the relatively small exposures with rapidly excreted substances, such as radioactive Hippuran, as compared to the exposures which result from conventional fluoroscopy and biplane angiocardiography, will serve to keep this problem in proper perspective.

Concluding remarks

It is to be emphasized that *no cardiac patient should be denied a necessary radiologic examination.* However, the following measures will help in achieving the goal of minimum exposure consistent with optimal care.

1. Fluoroscopy of pediatric cardiac patients as a routine procedure in office practice should not be performed. X-ray films usually supply adequate information.

*Estimation of total body exposure from such compounds as I^{131} albumin, Diodrast, and Hippuran can be determined by the following formula:

Dose beta (rads) = $73.8 \times \bar{E}p \times Co \times Teff$

Dose gamma (r) = $0.0346 \times p \times L \times Teff. \times \bar{g} \times Co.$

where $\bar{E}p$ = average energy per disintegration in mev., Co = original concentration in microcuries/Gm., Teff. = effective half life in days, p = density of absorbing medium, L = gamma ray dose rate constant, $\bar{g}$ = geometrical factor

Table I. *Age and sex distribution of 297 patients*

A. Patients who died without postoperative electrocardiogram

Age (yr.)	0–1	1–5	6–15	Total number
Male	2	10	4	16
Female	3	9	5	17
Total number	*5*	*19*	*9*	*33*

Age range: 3 mo. to 12 yr.

B. Patients with postoperative electrocardiogram

Age (yr.)	0–1	1–5	6–15	Total number
Male	3	44	99	146
Female	0	35	83	118
Total number	3	79	182	264

Age range: 3 mo. to 15 yr.

Group B. The mean age in this group was considerably over 5 years, and the cardiac defects tended to be less severe than those of Group A.

FREQUENCY OF ARRHYTHMIAS. Sinus tachycardia and infrequent isolated premature ventricular beats have been excluded from this analysis.

In Table III the cases of tetralogy of Fallot have been grouped according to the presence or absence of significant right-to-left shunts. The cases of ventricular septal defect have been divided according to the presence or absence of pulmonary hypertension (arbitrarily defined as a pulmonary arterial systolic pressure above 50 mm. Hg). The incidence of arrhythmias was found to be considerably different in the various groups. Thus, among cyanotic cases of tetralogy of Fallot the incidence was 43 per cent, whereas among the acyanotic cases it was only 12 per cent. Among the cases of ventricular septal defect the incidence was 41 per cent in those with pulmonary hypertension, and only 9 per cent in those with lower pulmonary pressure.

Arrhythmias did not occur in cases which did not require atriotomy or ventriculotomy, namely, aortic stenosis, valvular pulmonic stenosis, aortic-pulmonic window, aortic insufficiency with bicuspid valve, and supravalvular aortic stenosis.

TYPE OF ARRHYTHMIA. The classification and analysis of arrhythmias are complicated by the occurrence of different arrhythmias in the same patient at different times. *In the present study the arrhythmias* have been classified as complete atrioventricular block, apparent complete atrioventricular block, atrioventricular dissociation, partial atrioventricular block, nodal rhythm, and atrial fibrillation (Table III). Apparent complete atrioventricular block was diagnosed in cases of total independence of the atrium and ventricle if the length of the recording was not suf-

Table II. *Group A. Patients who died without postoperative electrocardiogram*

Diagnosis	*Number of cases*	*Cardiac arrest*	*Heart block*†	*Low cardiac output*
Tetralogy of Fallot	9	6	5	7
Ventricular septal defect with pulmonary hypertension	7	6	5	3
Complete transposition of great vessels	6	5	2	1
Miscellaneous*	11	8	3	2
Total *number*	*33*	*25*	15	13

Mean pump time: 108 min. (Range: 40 to 238 min.)

*Atrial septal defect with pulmonary hypertension, congenital aortic stenosis and postoperative aortic insufficiency; ventricular septal defect with patent ductus arteriosus, aortic stenosis, and atresia of mitral valve; isolated valvular pulmonic stenosis, pulmonary valve atresia with patent ductus arteriosus; ventricular septal defect with aortic insufficiency, ventricular septal defect with patent ductus arteriosus and pulmonary hypertension, ventricular septal defect with right pulmonary vein entering superior vena cava, and pulmonary hypertension; cor triventriculare with ventricular septal defect; ventricular septal defect without pulmonary hypertension.

†The diagnosis of heart block was made by the surgeon at the time of operation by direct observation and also was noted on the electrocardiogram on the Viso-Oscilloscope.

Clinical communications

Electrocardiographic findings after open-heart surgery in children

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Electrocardiographic alterations commonly occur in patients after open-heart surgery.[1] The present study was designed to identify possible relationships of these changes to the type of cardiac defect and the surgical technique used, and to make observations on the effectiveness of treatment and prognosis.

Case material

The case material consists of the 297 pediatric patients who underwent cardiac surgery utilizing the DeWall oxygenator[2] at the University of Minnesota Hospitals during the period from Jan. 1, 1958, to May 31, 1960. All patients had congenital cardiac defects, except one child with rheumatic mitral valvular insufficiency. The surgical technique utilized was that described by Lillehei and associates.[3]

The cases have been grouped into two principal categories and these will be analyzed separately (Table I). *Group A* consists of patients who died during the operation or in the early postoperative period, for whom no permanent electrocardiographic record was available (33 cases). *Group B* consists of patients in whom at least one routine electrocardiographic record of the standard and unipolar leads was taken in the first several hours after operation (264 cases).

Results

Group A. As shown in Table II, this group was composed mainly of patients with tetralogy of Fallot, ventricular septal defect with pulmonary hypertension, transposition of the great vessels, or combined defects. The average age was considerably under 5 years. The average time on the pump oxygenator was 108 minutes. All of these features tend to identify this group as one with a high surgical risk.

The surgeon frequently attributed the patient's death to cardiac arrest, heart block, low cardiac output, or combinations of these (Table II). The high frequency of cardiac arrest diagnosed in this group may be related in part to the severity of the preoperative cardiac status of these patients and the complexity of the anatomic defects which required repair. In about one half of the cases the surgeon made a diagnosis of heart block by direct observation at the time of operation. Death cannot necessarily be attributed to heart block per se, however, since the block may have been secondary to a more basic derangement in cardiac physiology.

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vealed ventricular capture. The initial tracings were then reclassified as showing atrioventricular dissociation without recorded ventricular capture. Thus, one such case listed in Table III did not show ventricular capture until the third postoperative day.

Table IV summarizes the analysis of various factors that appeared to be related to the frequency and type of arrhythmias. These factors include the diameter of the defect, duration of pump run, duration and type of cardiac arrest, and the nature of the surgical procedure. It is evident that with a larger size of septal defect, or longer duration of pump run or cardiac arrest, there was a higher incidence of arrhythmias. The use of patches in repairing defects also appeared to increase the incidence, but to a lesser degree.

The incidence of complete bundle branch block after surgery was also investigated (Table V). Patients with preoperative complete bundle branch block (American Heart Association criteria) were excluded. Complete right bundle branch block appeared postoperatively in 135 cases. Among the cyanotic cases of tetralogy of Fallot

Table IV. *Factors potentially contributing to the occurrence of arrhythmias (Group B)*

Diagnosis (Number of cases)	Arrhythmia	Cardiac arrest			No cardiac arrest	Duration of cardiac arrest*	Duration of pump run*	Diameter of septal defect†	Surgical patch	Stitch repair
		K	K+SH	SH						
Cyanotic TF (42)	Absent (24)	7	3	7	7	36 (10-80)	67 (32-118)	2.2 (1.3-3)	8	16
	Present (18)	8	2	7	1	57 (31-106)	91 (56-146)	2.5 (1.2-2.5)	3	15
Acyanotic TF (17)	Absent (15)	4	1	3	7	20 (4-36)	40 (26-57)	1.5 (0.4-3)	7	8
	Present (2)	1	0	1	0	25 (10-40)	70 (37-104)	1.7 (1.5-2)	1	1
VSD without PH (69)	Absent (63)	22	4	13	24	18 (6-35)	31 (12-79)	1.1 (0.3-3)	56	7
	Present (6)	0	0	5	1	26 (11-38)	41 (22-60)	2.4 (1.5-2.5)	5	1
VSD with PH (39)	Absent (23)	12	1	5	5	23 (9-45)	44 (17-74)	2.3 (0.4-3)	8	15
	Present (16)	7	1	7	1	35 (7-60)	52 (22-83)	2.9 (2.5-5.5)	3	13
ASD (30)	Absent (22)	0	0	0	22	—	28 (16-52)	2.9 (1.5-4)	18	4
	Present (8)	0	0	0	8	—	37 (18-58)	3.4 (3-5)	4	4
A-V canal (17)	Absent (11)	0	0	0	11	—	55 (55-76)	2.6 (1.5-4)	2	9
	Present (6)	0	0	0	6	—	74 (79-107)	2.2 (2.5-4)	2	4
Miscellaneous (50)	Absent (41)		20		21	20 (6-58)	56 (30-96)	—	—	—
	Present (9)		3		6	22 (6-34)	31 (12-106)	—	—	—

*Duration cardiac arrest and duration of pump run are given in minutes: mean duration with range in parentheses.
†Diameter of septal defect is given in centimeters: mean diameter with range in parentheses.
K: Potassium citrate. SH: Selective hypothermia. See Table III for other abbreviations.

Table III. Frequency and type of arrhythmias after intracardiac surgery (Group B)

Diagnosis	Number of cases	Apparent complete A-V block or complete A-V block		A-V dissociation		Partial A-V block		Nodal rhythm		Atrial fibrillation		Total number of arrhythmias	
		Number of cases	Died	Number of cases	Died	Number of cases	Died	Number of cases	Died	Number of cases	Died	Number of cases	Died
Cyanotic TF	42	10(23)*	7	4(9)***	1	3(7)	1	1(2)	1	0(0)	0	18(43)	10
Acyanotic TF	17	1(6)	1	0(0)	0	1(6)	0	0(0)	0	0(0)	0	2(12)	1
VSD without PH	69	0(0)	0	3(4)†	0	2(3)	0	0(0)	0	1(1)‡	0	6(9)	0
VSD with PH	39	5(13)	2	7(20)	1	2(5)	0	2(5)	0	0(0)	0	16(41)	3
ASD	30	0(0)	0	3(10)	0	3(10)	0	2(7)	0	0(0)	0	8(27)	0
A-V canal	17	2(12)**	1	3(18)	1	1(6)	0	0(0)	0	0(0)	0	6(35)	2
Miscellaneous§	50	3(6)	2	(12)	0	0(0)	0	4(4)	0	1(2)	0	9(18)	2
Total number	264	21	13	21	3	12	1	9	1	2	0	65	18
Per cent		8	62	8	14	5	8	3	11	1	0	25	28

TF Tetralogy of Fallot VSD Ventricular septal defect PH: Pulmonary hypertension ASD Atrial septal defect A-V: Atrioventricular

Numbers in parentheses are per cents

*One patient presented apparent complete A-V block for 15 days, then sinus rhythm for a short period, and then complete A-V block

**Both patients had the complete form of A-V canal

***This patient presented atrial fibrillation for a brief period

†Did not exhibit ventricular capture for 3 days

‡This patient showed partial A-V block for a short time after operation but then developed persistent atrial fibrillation

§The miscellaneous cases include. 1, With arrhythmia Ventricular septal defect with atrial septal defect, pulmonic stenosis with corrected transposition of the great vessels, ventricular septal defect with atrial septal defect and pulmonary hypertension, anomalous total pulmonary venous connection, mitral insufficiency corrected transposition with single ventricle- left ventricle-right atrial septal defect, cor triventriculare with ventricular septal defect and infundibular pulmonic stenosis, valvular pulmonary stenosis. II, Without arrhythmia Aortic stenosis (9), valvular pulmonic stenosis (7) combined valvular and infundibular pulmonic stenosis (4), isolated infundibular pulmonic stenosis (3), ventricular septal defect with atrial septal defect, aortic-pulmonic window (2); valvular pulmonic stenosis with atrial septal defect (2) subvalvular aortic stenosis, aortic insufficiency due to bicuspid valve, supravalvular aortic stenosis; cor biloculare, cor triatriatum, mitral insufficiency due to endocardial fibroelastosis, ruptured sinus of Valsalva, ventricular septal defect with atrial septal defect patent ductus arteriosus double mitral orifice, and pulmonary hypertension ventricular septal defect with ruptured sinus of Valsalva ventricular septal defect with coarctation of the aorta and dextrocardia infundibular pulmonic stenosis and ruptured sinus of Valsalva ventricular septal defect with supravalvular pulmonic stenosis right aortic arch, patent ductus arteriosus, and atrial septal defect

ficient for ruling out completely the possibility of atrioventricular dissociation due to advanced atrioventricular block. Cases of atrioventricular dissociation were attributed to interference whenever the ventricular rate was more rapid than the atrial rate, or to advanced atrioventricular block when a prolonged P-R interval was present in ventricular capture. The atrial rate was faster than the ventricular rate in the great majority of cases. In the classification of partial atrioventricular block, nodal rhythm, and atrial fibrillation, the classic electrocardiographic criteria were used.[3]

EVALUATION OF ARRHYTHMIAS. Patients very frequently presented different grades of conduction disturbances during the postoperative period. Thus, patients with partial atrioventricular block often showed transitions from 2:1 to 3:1 block to Wenckebach phenomenon. In some cases of atrioventricular dissociation due to "advanced atrioventricular block" the electrocardiographic pattern passed through different types of second-degree or first-degree atrioventricular block before returning to normal. Similarly, in some patients with partial atrioventricular block there was a period of first-degree block before normalization occurred.

Among cases initially viewed as apparent complete atrioventricular block there were 7 in which the later electrocardiograms re-

operative period, the occurrence of occasional ventricular captures indicates a more favorable prognosis. Thus, of 21 patients with apparent complete atrioventricular block, the 7 who subsequently showed ventricular captures all survived, whereas only 5 of the 14 who did not show ventricular captures survived. However, the presence of a premature ventricular beat may be misinterpreted as such a "capture" and a good prognosis expected, whereas it indicates, instead, increased ventricular irritability and increased risk. Alternating arrhythmias may occur, and in these the interpretation is facilitated by longer and more frequent electrocardiographic tracings. For example, in one case there was at first an apparent complete atrioventricular block for 15 days, then a short period of sinus rhythm, and finally a classic pattern of complete atrioventricular block with a slow ventricular rate of 40 (Table III, case indicated by an asterisk).

Postoperative arrhythmias, such as nodal rhythm, tend to be transitory in cases of atrial septal defect, and perhaps are related to temporary edema of the atrioventricular nodal region. In contrast, arrhythmias which develop after closure of ventricular septal defects tend to be of long duration or permanent, probably as the result of more serious trauma to the conducting bundle by needle or suture.

This report is not primarily concerned with the treatment of postoperative arrhythmias. However, it should be mentioned that injudicious treatment may aggravate the arrhythmia already present. Thus, in cases of atrioventricular dissociation due to advanced atrioventricular block or to interference the use of Isuprel may further the difficulty. In some cases of pseudoarrhythmias due to competition between the electrical and physiological pacemakers, discontinuance of the electrical pacemaker will improve the situation. The electrical pacemaker is, of course, a valuable means for producing an adequate cardiac rate and cardiac output in patients with complete atrioventricular block until the time that the rhythm reverts to normal or the body adjusts to the slow rate.[9,10] The occurrence and treatment of postoperative complete atrioventricular block has been recently dealt with in detail by Lauer and associates.[11]

Arrhythmias in which there is a varying response of the ventricle to the supraventricular centers are generally of little significance and usually require no specific therapy. This is true also of the majority of cases of atrioventricular dissociation in which the ventricular rate is adequate. In these cases it appears advisable to merely observe the gradual resumption of normal cardiac conduction. The development of complete right bundle branch block after corrective surgery likewise requires no specific treatment.

In regard to postoperative complete right bundle branch block, cases with preoperative right ventricular hypertrophy generally showed a Type I pattern (classification of Lepeschkin). On the other hand, those with predominant left ventricular hypertrophy preoperatively showed Type III. This observation offers support for the viewpoint that a diagnosis of right or left ventricular hypertrophy can be made in the presence of complete right bundle branch block.

Summary

The records of 297 pediatric patients who underwent intracardiac surgery using the pump oxygenator were reviewed in regard to the incidence and type of postoperative arrhythmias. Of the 33 patients who died during or just after operation without a permanent electrocardiogram having been taken, 15 were noted by the surgeon to have a complete heart block. This group of 33 patients was characterized by young age, severe defects, and long run on the pump oxygenator, in contrast to the other 264 patients who tended to be older, to have milder defects, and to have shorter pump runs.

Arrhythmias occurred only after atriotomy or ventriculotomy, and were more common in the cyanotic cases of tetralogy of Fallot and in those cases of ventricular septal defect with pulmonary hypertension. The incidence of postoperative arrhythmias varied directly with the size of the septal defect, the duration of pump run or cardiac arrest, and, to a lesser degree, the use of patches in repair.

There were 21 cases of complete atrio-

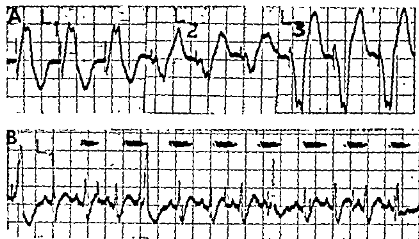


Fig. 1 *A*, Patient A.R., 5 years old. Pacemaker on. Pacemaker impulse inscribed as sharp initial deflection. Tracing shows left bundle branch block pattern *B*, Patient D.J., 8 years old. Pacemaker on. Bizarre QRS complexes are produced by pacemaker. (Pseudopremature ventricular contractions.)

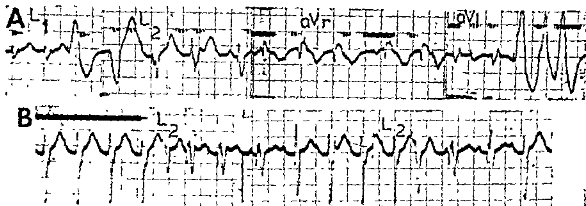


Fig. 2 *A*, Patient S.A., 9 years old. Pacemaker on. Pseudopremature ventricular contractions except for last two in run of three on Lead aV$_R$, which are true premature ventricular contractions. *B*, Patient C.R., 5 years old. Pacemaker off in first portion (*beneath heavy line*), with sinus rhythm. Remainder with pacemaker on, showing competition between electrical pacemaker and sinoatrial node.

instances of atrioventricular dissociation, partial atrioventricular block, or nodal rhythm. The two occurrences of complete atrioventricular block in this group were in patients who had atrioventricular canal with a ventricular septal defect component. As noted by others,[4-7] complete right bundle branch block developed only after closure of ventricular septal defects. The development of such block has been attributed by some to the ventriculotomy rather than to the closure of the defect.[8] In this regard, in one of the present cases, complete right bundle branch block developed in a female patient in whom closure of the ventricular defect had been performed through the tricuspid orifice after atriotomy; this patient did have a preoperative incomplete right bundle branch block pattern, however. Apparently, right bundle branch block may develop as a result of either ventriculotomy or surgical manipulation in the area of the membranous ventricular septum. Interestingly, we have observed the development of complete left bundle branch block after left ventriculotomy for aortic stenosis.

If there is relative independence of the atria and ventricles in the immediate post-

Thrombelastographic study of 76 patients on long-term anticoagulant therapy with coumarin-type drugs

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Investigators have repeatedly concluded that the one-stage prothrombin test is highly reproducible and remains the most adequate test for clinical evaluation of the effect of coumarin-type anticoagulants. Specific assays for the degree of reduction of prothrombin (Factor II), proconvertin (Factor VII), Stuart-Prower factor, and plasma thromboplastin component (Factor IX), in patients on coumarin-like drug therapy have shown that the prothrombin levels bear no relation to the reduction in other factors in any given patient on any given dosage of the drug.[1,2] Nevertheless, the opinion stands that the one-stage "prothrombin" test does give an approximate estimation of the degree of effective anticoagulation, and that, although not ideal, it is satisfactory for clinical purposes in the majority of patients.

In addition to alteration of the production and/or activity of these several coagulation proteins, the effect of the coumarin-like drugs on platelet clumping and adhesiveness has been found to be considerable.[3] These drugs lower the adhesive index and prolong platelet clumping time to a highly significant degree.[4,5] If then, the prothrombin time is to serve as the approximate estimation of the degree of effective anticoagulation, it would seem to be important to establish in each patient separately the reliability of the test as a measure of the behavior of the clotting mechanism as a whole. For those in whom the test does seem reliable, an individual "therapeutic range" might be established. The whole problem of the adequacy of the anticoagulant therapy would seem to relate directly to the adequacy of dosage of the coumarin-like drug, the measure of which is generally left entirely to the clinical laboratory. Indeed, these patients may be owing their lives (or the threat of loss of it) to a laboratory technologist whose skill, resourcefulness, and conscientiousness in performing whatever "prothrombin time" test is chosen is obviously the single most important factor in the laboratory control of anticoagulant therapy.

Because of the difficulty in assaying each element which is altered by the drug therapy, and because we are interested in the summary effect of all these changes on the coagulation mechanism, thrombelastography appears to be the ideal tool for evaluation of the one-stage protrombin time as an adequate measure for the control of this anticoagulant therapy.[6]

The Thrombelastograph (TEG) (Fig. 1),

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ventricular block among these 264 patients who had postoperative electrocardiograms, with death ensuing in 13. Just as in the smaller group of 33, this complication commonly developed in patients with cyanotic tetralogy of Fallot or ventricular septal defect with pulmonary hypertension. No cases occurred after repair of atrial defect, although it appeared in 2 patients with atrioventricular canal of the complete type.

Complete right bundle branch block developed in the majority of patients who had a ventricular septal defect or atrioventricular canal, particularly if incomplete right bundle branch block was present preoperatively.

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IX), Owren developed a new reagent,* Thrombotest,[11-14] which is sensitive to alterations in the level of all the coagulation protein factors known to be influenced by oral anticoagulants. Thrombotest determinations were done in triplicate on each of the plasmas under study, thus providing an arbiter in comparing the routine laboratory one-stage results with the thrombelastographic values obtained in each patient.

3. The thrombelastographic pattern was measured simultaneously on a fresh sample of citrated plasma, in duplicate.

Questionnaires (like that shown on page 743) for obtaining clinical information were sent out to the physicians in charge of each patient who had been studied. In many instances, serial determinations were made, in which cases follow-up questionnaires were submitted. The study was done without the physician in charge of the individual patient having knowledge of these results, so that each physician would continue to use his usual judgment (based on the "prothrombin time" value from the clinical laboratory) in fixing the dose of the anticoagulant drug.

As the study progressed and the thrombelastographic patterns of patients on anticoagulant therapy accumulated and were compared with the patterns of clinically significant spontaneously occurring defects, certain conclusions evolved. It became evident that patients who have only slight *r* value prolongation reflecting their anticoagulant therapy are not at all "anticoagulated," since such minor changes were never correlated with any evident problem in forming the clot whenever one was necessary.

Generally, after a fair degree of *r* value prolongation has been induced, one sees a prolongation in the *k* value in the thrombelastogram. It seemed that an *r* value of 30 to 40 mm. (15 to 20 minutes) and a *k* value of 12 to 20 mm. (6 to 10 minutes) represented an ideal state of anticoagulation to be maintained. If the amount of the drug is raised in a patient who is in the "ideal situation," one finds a "pulling in" or a narrowing of the *ma* value. This state obviously represents an "overshooting," and the patient thus possesses the pattern of those patients with spontaneously occurring coagulation problems who frequently and easily get into serious problems with hemorrhage.

When the thrombelastographic *r* value is plotted against the routine one-stage prothrombin time in per cent of normal control, a "scatter graph" is obtained, reflecting poor correlation (Fig. 3).

When the thrombelastographic *r* value is plotted against the Thrombotest time results, an "L"-shaped curve is obtained, with a "bunching" of the values at the bow of the "L." In other words, when the Thrombotest value gets below 20 per cent of normal, the *r* values quickly rise above the 20 mm. normal point and scatter up through the 50 mm. (25 minutes) area (Fig. 4).

When the thrombelastographic *k* value is plotted against the routine one-stage prothrombin time in percentage of normal control, there is a better degree of correlation than is obtained with the *r* value, but the values are skewed toward the

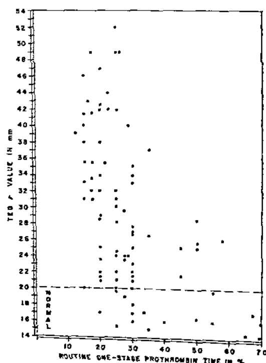


Fig. 3. The thrombelastographic *r* value plotted against the one-stage prothrombin time result.

*This reagent has been kindly supplied by Dr. Olav Biörnson, Nyegaard and Company, Oslo, Norway.

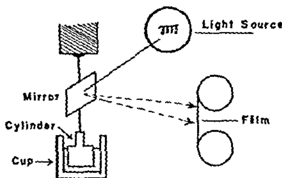


Fig. 1. Schematized mechanism of the Thrombelastograph. The cup is motor driven to oscillate 4 degrees and 45 minutes on its own axis back and forth every 9.0 seconds. A sample of plasma is placed in the cup, recalcified, and the recording begun.

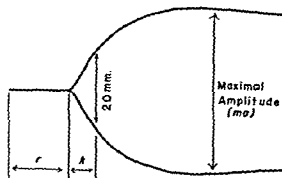


Fig. 2. Scheme of a normal thrombelastogram. The reaction time (*r*) indicates the time interval between recalcification of plasma and the first signs of resistance. The clot formation time (*k*) is that section of the curve which lies between *r* and a point where the curves are 20 mm. apart. The maximal amplitude (*ma*) is value related to clot elasticity.

designed by Hartert,* provides more information on fibrin formation than does any other method. This instrument can record continuously and simultaneously fibrin formation of three blood or plasma specimens and provide a permanent record photokymographically (Fig. 2). The exact procedure for thrombelastography is described adequately elsewhere.[7-10]

Our specific modifications, adapted because of the procedure necessary in obtaining samples of plasma, are as follows: (1) In obtaining the sample of plasma, one part of sodium citrate (3.8 per cent) is added to four parts of whole blood. This sample is immediately centrifuged at 800 to 900 r.p.m. for 5 minutes. (2) 0.25 ml. of plasma is placed in the cell, and 0.1 ml. of calcium chloride (3.9 mM.) is added. (3) The mixture is covered with mineral oil, and recording is begun.

A plan for establishing a definition of "ideal anticoagulation" based on summation of induced defects thrombelastographically measured

Phase 1. Normal subjects. Thrombelastographic patterns showed clear-cut end points for normal values: *r* value—not above 20 mm. (10 minutes); *k* value—not above 8 mm. (4 minutes); *ma* value—not less than 54 mm.

Phase 2. The measure of spontaneously occurring coagulation defects, congenital and acquired, in which clinically significant bleeding occurs. This group included observation on patients with all degrees of thrombocytopenia, thrombasthenia, and classic hemophilia (Factory VII), PTC deficiency (Factor IX), advanced liver disease, circulating anticoagulants associated with connective tissue disease, fibrinogenopenia, fibrinolysis, as well as uremia and other strictly vascular hemostatic defects.

Phase 3. Thrombelastographic measure of the defects induced by therapy with a coumarin-type drug. In this series there were 64 patients (84.2 per cent) taking warfarin sodium (Coumadin), 9 patients (11.8 per cent) taking phenprocoumon (Liquamar), and 3 patients (4 per cent) taking bishydroxycoumarin (Dicumarol).

All of these three phases of the study were going on simultaneously, and from the onset all blood samples were studied accordingly:

1. The values obtained by the technologist in the routine laboratory performance of the one-stage prothrombin time were accepted as the basic standard since this determination is used by the clinician in regulating the dosage of his patient's therapy.

2. Because of the insensitivity of most commercially available thromboplastic substances toward quantitative alterations in plasma thromboplastin component (Factor

*Manufactured in West Germany by Fritz Hellige and Company for Haemoscope Corporation, Albertson, Long Island, N. Y.

Anticoagulant Research Project Questionnaire

Physician in charge: ______
Name of patient: ______
Date (through which these answers apply) ______

1. Age of patient: ______
2. Diagnosis for which long-term anticoagulant therapy was indicated:
   ASHD ______
   Cerebral vascular disease ______
   Recurrent thrombophlebitis ______
   Other (specify) ______
3. Date anticoagulant therapy begun: ______
4. Drug used:
   Coumadin ______
   Dicumarol ______
   Other (specify) ______
5. Usual maintenance dosage: ______mg./day
6. Character of control as judged by prothrombin time:
   Erratic ______
   Smooth ______
7. Any evidence of functional kidney impairment now? ____yes____no.
8. Any evidence of liver disease? ____yes____no.
9. Any "overshooting" clinically recognized?
   ____yes____no.
   Purpura? ______ Date: ______
   Hematuria? ______ Date: ______
   Other (specify) ______ Date: ______
10. What has been your intended level of control in per cent of normal control?
    10–15% ______ 20–25% ______
    15–20% ______ 25–30% ______

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serve as a platelet substitute in the thrombelastographic system as it will in some "thromboplastin generation test" systems.

After accumulation of the data on 76 patients it was possible to see definite trends and relationships. These observations alone allow one to gain a conviction in regard to what constitutes ideal alteration of the coagulation mechanism to such a degree that the patient is suitably, although safely, protected against thromboembolic phenomena in so far as this class of drugs is able to effect alterations. There are indications that the prolongation of the *r* value alone in the thrombelastographic pattern does not constitute a significant state of anticoagulation. Prolongation of the *r* value and *k* value is probably ideal. These induced abnormalities plus the narrowing of the *ma* value seem to reflect a dangerous state of anticoagulation, since spontaneous purpura and hematuria are frequently associated with this alteration. Thus, making the arbitrarily established definitions, we are able to group patients into three categories: (1) ideally anticoagulated, (2) not protected, and (3) overdosed.

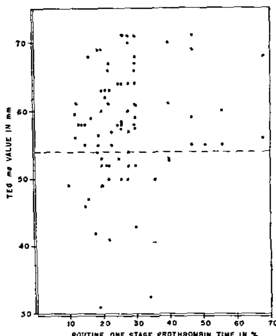


Fig. 7. The thrombelastographic *ma* value plotted against the one-stage prothrombin time result.

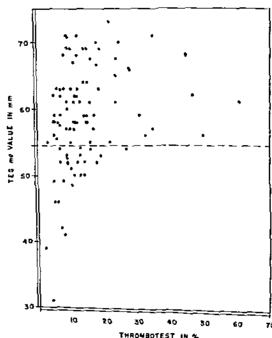


Fig. 8. The thrombelastographic *ma* value plotted against the Thrombotest result.

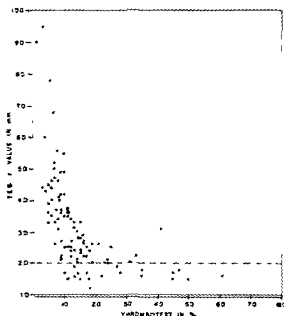


Fig. 4. The thrombelastographic *r* value plotted against the Thrombotest result.

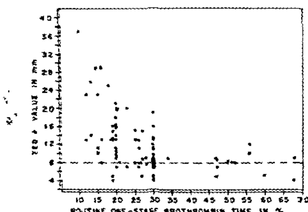


Fig. 5. The thrombelastographic *k* value plotted against the one-stage prothrombin time result.

higher "prothrombin time" results, indicating that the "prothrombin time" lacks sensitivity in reflecting significant *k* value prolongation (Fig. 5).

When the thrombelastographic *k* value is plotted against the Thrombotest time results, a very fine "L"-shaped curve with bunching of the values at the bow is obtained. As the values get further below the 20 per cent value with the Thrombotest, the majority of the determinations show a *k* value spread up toward the 30 mm. level. Correlation is good (Fig. 6).

When the thrombelastographic *ma* value is plotted against the routine one-stage prothrombin time, another poor correlation scatter graft is obtained (Fig. 7).

Finally, when the thrombelastographic *ma* value is plotted against the Thrombotest time results, a highly significant bunching of the points is located below the 20 per cent Thrombotest level (around the 10 per cent therapeutic range) and above the 54 mm. *ma* value level. All of the *ma* values below the "dangerous" 50 mm. level fall in the area of less than 10 per cent by the Thrombotest measurement, that is, below the therapeutic range (Fig. 8).

These data reflect the better correlation between Thrombotest results and all facets of the thrombelastographic pattern analysis than is found between the routine one-stage prothrombin test and these facets. If the interpretation of thrombelastograph's in vitro documentation of in vivo events is worthy of endorsement, then it *must follow* that *Thrombotest* is a superior reagent for measuring alterations in coagulation protein activities (but no platelet changes) induced by coumarin-type drug therapy. Whenever divergence between thrombelastographic patterns and Thrombotest results have been observed, it has been naturally interpreted as being due to platelet alterations which only thrombelastography can document. Further investigations to elucidate this contention are in progress. Studies with Inosithin indicate that this substance will not

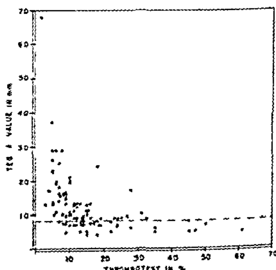


Fig. 6. The thrombelastographic *k* value plotted against the Thrombotest result.

some sort of direct relationship to the thrombelastographic pattern in the individual patient. In this case, the "therapeutic range" could be accurately determined for maintenance of that given patient by the "prothrombin time" alone. A natural extension of this study will be a long-term follow-up of that group of patients who are judged to be "not protected" for comparison with those considered to be in the "ideal range," in order to record the incidence of recurrent thromboembolic disease. This would be the application of the only clinical "end point" to the "test tube" phenomena. In all other published studies wishing to disclaim the value of anticoagulant therapy, patients are listed either as being "anticoagulated" or "not treated." These studies using thrombelastography would indicate that at least 46 per cent of the patients in the "anticoagulated" group would more properly be placed in the "untreated" group. In other words, it would seem that any statistical evaluation of what happens to patients on or off anticoagulant therapy would necessarily require a much more critical definition of what induced coagulation defects are expected to be measured in vitro.

Conclusions

Thrombelastography and Owren's Thrombotest have been compared with the routine laboratory prothrombin time in 76 patients on anticoagulant therapy with a drug of the coumarin type. By reference to thrombelastographic patterns obtained in any clinically significant spontaneously occurring coagulation defect, a thrombelastographic pattern considered to be idéal for a patient with a therapeutically induced coagulation defect was arbitrarily defined. The grouping of patients was entirely on the basis of the pattern of their thrombelastograms, with no reference to any clinical events; 34.2 per cent of these patients were judged to be ideally controlled, 46 per cent of these patients had no defects or only minor defects induced in the thrombelastographic pattern, and 19.8 per cent were considered to be, perhaps, dangerously overdosed. Further observations on a larger series of patients is indicated to establish the place of thrombelastography in the control of anticoagulant therapy.

I wish to thank Miss Jeanne Clark for her technical performance in this study.

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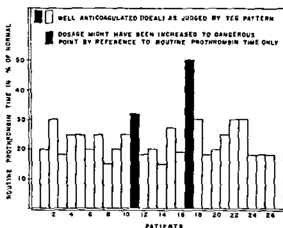


Fig 9. The one-stage prothrombin time results (in per cent of normal control) of the "ideally anticoagulated" group as determined thrombelastographically.

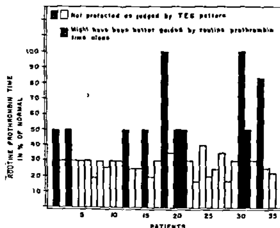


Fig 10 The one-stage prothrombin time results (in per cent of normal control) of the "not protected" group as determined thrombelastographically.

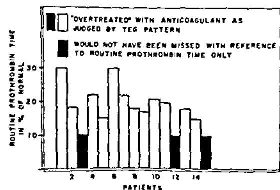


Fig. 11. The one-stage prothrombin time results (in per cent of normal control) of the "overdosed" group as determined thrombelastographically.

In a tabulation of the results obtained and conclusions drawn in the study of these 76 patients, Figs. 9, 10, and 11 display the data. In the "ideally anticoagulated group" (34.2 per cent of the total) there were only 2 patients whose one-stage prothrombin time was above 30 per cent of normal. By reference to the routine studies alone the physician might have increased the anticoagulant drug dosage and thereby placed these patients in the "overdosed" group. In the "not protected" group (46 per cent of the total) there were 11 patients (one third of this subgroup) who might have had their dosage increased to place them in the "well anticoagulated" group by reference to the one-stage prothrombin time alone; however, the physician chose to maintain this level. In the "overdosed" group (19.8 per cent of the total) there were only 3 patients who were at or below the 10 per cent level with the one-stage test; the remainder of the patients in this group would have been (and were) left on their current dosage by reference to the one-stage test only.

It is to be emphasized that the thrombelastographic pattern does not deliver figures with which strict formulas of good dosage can be applied. In each situation the pattern must be studied and interpreted. Although the normal *r*, *k*, and *ma* values never overlap with the induced abnormal, the exact degree of alteration of these three values under the influence of coumarin-type drug therapy must be considered as they relate to one another.

Summary

Coumarin-type anticoagulant agents have been in use for about 20 years, and their effect is primarily intended to be prophylactic in forestalling extension of existing clots and in preventing new thrombosis. The clinical "end point" in judging the effectiveness of such therapy must lie in the observation of whether there is recurrent thromboembolic disease. If one can accept the fact that the over-all clotting tendency as measured with the thrombelastograph bears a direct relationship to in vivo coagulability, then the system of controlled artefacts known as the "prothrombin time" should be used as a control measure only if it varies with

gauge transducers and the Electronics for Medicine photographic recorder. A few recordings were made on the Sanborn two-channel direct-writer. The pressures and oxygen saturations in the right ventricle and systemic artery were not all obtained simultaneously. Angiocardiograms were recorded by the Elema-Schonander biplane film changer, and using the Gitlund injector for the intracardiac injections of contrast media. All injections were made selectively into the outflow portion of the right ventricle unless otherwise specified.

The murmurs are described by intensity, location, and duration; the classification of Leatham[13] is employed. The clinical auscultation was correlated with phono-







Fig. *1*. *A*, Left lateral angiocardiogram shows a wide, anteriorly displaced aorta in Fallot's tetralogy (Patient R.C.) *B*, The photograph on the left shows greater density and earlier filling of the aorta and partially transposed aortic root; that on the right shows a wide base and ascending portion of aorta and small pulmonary arteries (Patient R C.).

The differentiation of pulmonic stenosis, ventricular septal defect with normal aortic root from tetralogy of Fallot

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Fallot, in 1888, described and correlated the clinical-pathological findings of the cyanotic congenital cardiac abnormality of pulmonic stenosis, interventricular septal defect, enlarged right ventricle, and overriding aortic root. Sixty years later the physiology of this congenital cardiac defect was clarified by studies which made use of the cardiac catheter.[2-4] It was also recognized that not all patients with tetralogy of Fallot were clinically cyanotic.[5] Several authors have distinguished between pulmonic stenosis (PS), ventricular septal defect (VSD) with overriding aorta and PS,VSD with normal aortic root.[6-8]

In recent years, however, there has been an attempt to classify all ventricular septal defects with narrowing of the right ventricular outflow tract, whether infundibular and or valvular PS, as being within one spectrum of the same lesion.[9-11] The purpose of this paper is to document the thesis that there are two distinct entities, both with acyanotic and cyanotic components, which are, clinically and physiologically, distinguishable: (1) PS,VSD with partially transposed aorta or overriding aortic root (tetralogy of Fallot), and (2) PS,VSD with normal aortic root.

Materials and methods

This study is an analysis of the clinical and laboratory data of patients with pulmonic valvular and/or infundibular stenosis, with ventricular septal defects, whose right ventricular pressures are at least equal to the systemic pressure. There are 17 patients with overriding aortic root and 18 with normal aortic root. No attempt at selection was made other than to choose patients whose data for analysis were available in as many parameters as possible. Surgical and/or postmortem data are presented when available. Postmortem examination was obtained in all patients who died.

All patients were studied by the technique of catheterization of the right side of the heart. The blood oxygen saturations were obtained by the Waters-Conley oximeter and/or by the manometric method of Van Slyke and Neill. Intracardiac pressures were recorded using Statham strain-

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Murmurs	*ECG*	*X-ray films and/or fluoroscopy*
Grade 3 harsh systolic 2-4 ICS	RAD, RVH	Normal-sized heart, clear lung fields, RA – ++, RV +, concave PA, "Coeur en sabot"
Grade 2 systolic, 3rd LSE	RAD, RVH, RA enlarged	Normal-sized heart, normal lung fields, RA – +, RV – +
Ejection systolic, 2nd ICS	RAD, RVH	Normal-sized heart, lung fields clear, RV +
Systolic, 4th ICS	RAD, RVH	Normal-sized heart, hypovascular lung fields, small PA
Grade 2-3 systolic, 3-4th ICS	RAD, RVH	Small heart, clear lung fields, RV ±
Grade 2 systolic, 2-3rd ICS	RAD, RVH	Normal-sized heart, clear lung fields, RA – +, RV +, "coeur en sabot"
Short Grade 2 ejection systolic, 2-3rd ICS	RAD, RVH, RA enlarged	Small heart, small PA, ultra clear lung fields, RV – +
Grade 3, ejection systolic, 2 ICS	RAD, RVH	Normal-sized heart, clear lung fields, RA +, RV +, slightly prominent aorta
Grade 3 systolic, 3rd ICS	Vertical heart. Normal ECG	Normal-sized heart, clear lung fields
Harsh Grade 3 systolic, pulmonary area	RAD, RVH	Normal-sized heart, clear lung fields, small PA, RV – +, right aortic arch
Ejection systolic, pulmonary area	RAD, RVH	Small heart, clear lung fields, RV +, concave PA
Ejection systolic, pulmonary area	RAD, RVH	Normal sized heart, clear lung fields, RA – +, RV +, "coeur en sabot," concave PA
Ejection systolic, pulmonary area, suggestive of holosystolic, 4th LSE. Continuous murmur at ductus area	RAD, RVH, LVH	Slightly enlarged heart, lung fields normal, LA ++, RV +, aorta wide
Grade 2 systolic, 2-3rd LSE	RAD, RVH	Normal-sized heart, lung fields clear, RV ++
Ejection systolic	RAD, RVH	Normal-sized heart, lung fields normal, RV +
Small ejection systolic. Ejection click	RAD, RVH	Normal-sized heart, lung fields slightly hypovascular, RV +
Ejection systolic. Grade 2-3, LSE	RAD, RVH	Normal-sized heart, normal pulmonary vasculature

respectively. RA: Right atrium. RV. Right ventricle PA: Pulmonary artery

sistently enlarges. Most likely, this is due to the enlarging of the left ventricle, which receives a normal flow of blood after corrective surgery (Fig. 2).

Pulmonic stenosis with interventricular septal defect with normal aortic root. Anatomically, those with a normal aortic root fall into two categories (Table IIC). There are those who developed valvular pulmonic stenosis and interventricular septal defect in utero and often had an associated hypertrophy of the infundibular area (G.L., C.C., D.E., M.L.M., R.C., H.A.). The majority of our patients were undoubtedly born with isolated ventricular septal defect and developed infundibular hypertrophy months to years after birth, as reported by Gasul and associates.[10] In only S.G., R.C., and E.B. is there adequate clinical or cardiac catheter evidence for this mechanism (Fig. 3). R.C. and E.B., who had pulmonary valvular stenosis, also developed muscular hypertrophy of the outflow tract of the right ventricle with time[22] (Fig. 4).

The physical findings of ventricular septal defect with a left-to-right shunt, as well as pulmonic stenosis, were the features that distinguished the acyanotic patients with a normal aortic root from the minimally cyanotic or acyanotic patients with Fallot's tetralogy. As in Fallot's tetralogy, the sound of pulmonic closure is diminished or absent. Even in those patients with a significant increase in pulmonic flow, the pulmonic sound may be diminished (D.R., R.B., R.C., R.K., A.J., C.C., E.B.). In patients with balanced or right-to-left shunts the auscultatory findings may be indistinguishable from those in patients of the Fallot group.

There are, however, other indices that

Table IA. Tetralogy of Fallot

Name	Age	Sex	Cyanosis	Growth	Thrills	Sounds
K.B.J.	2	F	Yes	Poor	4th ICS	Single 2nd
D J.	28	F	0	Normal	±	Single 2nd
C S.	9	M	Yes	Normal	Systolic	Single 2nd
J.N.	30	M	Yes	Normal	0	P_2 diminished
R.C.	4	F	Yes	Small	Systolic, 3-4 ICS	Loud single 2nd
S.S	16 mo.	F	Yes	Small	None	Single 2nd
M.S.	3	F	Yes	Normal	Systolic, pulmonary area	Single 2nd
M O	9	M	Slightly	Normal	Systolic, 2-3 ICS	Single 2nd
I A.	26	F	At times	Normal	Systolic, LSE	P_2 diminished
E F	5	F	Yes	Normal	±	Single 2nd
B J	5	M	Yes	Normal	2nd ICS	Single 2nd
D.H.	8	M	Yes	Poor	0	Single 2nd
C C	18 mo.	M	0	Poor	Systolic, pulmonary area	Single 2nd
R M	15 mo	M	Yes	Poor	Systolic	Single 2nd
D E	30	M		Normal	0	Single 2nd
F M.	7	M	Yes	Poor	0	Single 2nd
J M W	21	F	Slightly	Normal	0	Single 2nd

ICS Intercostal space LSE Left sternal edge RAD Right axillary deviation RVH and LVH. Right and left ventricular hypertrophy.

cardiograms when possible. Standard twelve-lead electrocardiograms and Lead V_{3R} were analyzed.[14-19] An *A* wave in the right atrial tracing was considered to be dominant when it was 4 mm. above the *V* wave and had a rapid *X* descent.

Results

Tables IA, IB, IC, and IIA, IIB, IIC summarize the data in the two groups of patients. The important feature that distinguishes the two entities is the hyperdynamic left ventricle in the group with the normal aortic root.

Tetralogy of Fallot. The findings in Fallot's tetralogy are well known,[6,11,17,19,20,21] but certain observations should be emphasized: (1) Patients with tetralogy of Fallot have normal-sized or small hearts, which do not show progressive enlargement with time; there are no progressive changes in the electrocardiogram of these patients after infancy, and cardiac failure is uniformly absent. (2) A dominant *A* wave does not occur in this group.[6,17] (3) There is little or no evidence of a left-to-right shunt at the ventricular level, and the pulmonary arterial pressures are either normal or below normal.

In our experience with selective angiocardiograms with rapid injection of the dye into the outflow tract of the right ventricle, the large aortic root can usually be seen to fill earlier than, or at least simultaneously with, and to have a density equal to, the pulmonary artery. In most cases the dextraposed origin of the aorta is usually recognized (Fig. 1). A small pulmonary artery is sometimes noted but not consistently enough to be of diagnostic value.

Postoperatively, the Fallot heart con-

Aorta		Left ventricle		Left atrium		Angiocardiogram
S/D	Sat. (%)	S/D	Sat. (%)	S/D	Sat. (%)	
						Simultaneous filling of aorta and pulmonary artery. Dextroposed aorta and wide base. Jet from RV to aorta seen
						Aorta slightly wider than normal and (?) dextroposed
						Venous angiocardiogram
						Marked dextroposed aorta
						None
82/57		93/1	79			Simultaneous filling of aorta and pulmonary artery Wide dextroposed aorta
						None
118/80	86					Slow injection, PA fills earlier than aorta; aorta anterior to normal location and wide at base Valvular stenosis
						Venous angiocardiogram, wide aortic base and dextroposed aorta, PA fills before aorta
						None
		100/0	87			Venous angiocardiogram, early and simultaneous filling of aorta and pulmonary artery
						Simultaneous filling of aorta and pulmonary artery. Dextroposed aorta
Catheterization performed on 100% oxygen						None
						None
				10	PW 99	None
108/31 95/70	69		97		94	PA and aorta filled simultaneous, large aortic root, anterior position of aorta, suggestive of infundibular stenosis, injection into right atrium
						PA fills before aorta; LV fills from RV. Aortic root slightly wider than normal
						Simultaneous filling of pulmonary artery and aorta. Aorta wide and somewhat transposed. Pulmonary valvular stenosis Suggestion of infundibular stenosis

PW: Pulmonary wedge. NF Not entered PA Pulmonary artery

evidence of left as well as of right ventricular hypertrophy as suggested by the diphasic complexes in the precordial leads (H.A., W.F., J.B.), (Fig. 10) pointed to an associated ventricular septal defect.

A dominant *A* wave was seen in 9 of the 11 patients with a normal root who had normal pulmonary arterial pressures, and in 2 of the 5 with increased pressures in the pulmonary artery (Fig. 11). Data were not available in 2 patients. Adequate information is not available to explain the differences in the *A* waves between the patients with Fallot's tetralogy and those with a normal aortic root.

Acyanotic or minimally cyanotic adults with Fallot's tetralogy were the most difficult to classify. D.J. and J.M.W. fit the criteria for the diagnosis in this group, although in J.M.W. the aorta did not fill simultaneously with the pulmonary artery. The left ventricle of the patients in this group may not be hyperactive, but it is undoubtedly well developed because of the minimal degree of overriding.

Postoperatively, the hearts of patients with a normal aortic root have not shown enlargement; however, neither have they shown a decrease in size. One factor is the relatively short time since operation, and another explanation in some patients may be the persistence or reopening of a ventricular septal defect. In 2 patients, repeat cardiac catheterization has demon-

Table 1B. Tetralogy of Fallot

Name	Age	Sex	SVC (% Sat)	IVC (% Sat.)	Right atrium			Right ventricle		Pulmonary artery		Systemic artery	
					A	V	Sat. (%)	S/D	Sat. (%)	S/D	Sat. (%)	S/D	Sat. (%)
K B J	2	F	68	67	4	2		88/8	67	16/10		130/73	84
D J	28	F	60		10	8	67	90/0	64	20/10	67	79/47	92
C.S	9	M	52	49	6	4	61	96 0	50		50	90/59	65
J.N.	30	M	49	48	8	6	50	128/2	48	25/6	50	120/74	77
R C.	4	F	51	67	6	3	62	94/0	60	NE 15/? at operation		110/77	81
S S	16 mo.	F		50			46	73/7	48	12/2	48	100/5	71
M S.	3	F	49	53	9	8	55	87/10	58	13/7	50	92/73	76
M O	7	M	69	69	Rate 150 single wave			102/5	69	23/4	72	125/78	93
I A	28	F	66		7	4	65	86/4		12/5	71	100/58	89
E F	5	F	57	66	9	7	64	97/2	63	12/5		110/73	83
B J	5	M	65		5	3	66	87/0	67	18/3	67	109/56	84
	7		77	74	11	10		120/5		NE		109/62	83
D H	8	M			Rate 150 single wave		68	81/12	70	9/2	72	83/50	87
R M	15 mo	M	69		12	10	65	95/0	69	25/12	65	101/64	90
C C	18 mo	M	67		6		65	100/0	79	35/18	85	100/45	97
F M	7	M	51		8	7		100/0	54	NE		105/65	68
J M W	21	F	63		5	3	64	123/7	69	14/5	68	115/78	85
D E	30	M			9	6	52	120/5	50	NE	52	120/88	76

SVC: Superior vena cava. IVC: Inferior vena cava. Sat.: Saturation. A: Atrial A wave. V: Atrial V wave. S/D: Systolic over diastolic

reveal the distinctive physiologic differences. Cardiac fluoroscopy or x-ray examination usually demonstrated the evidence of a hyperdynamic left ventricle by the presence of an enlarged left ventricle and/or left atrium. Almost uniformly the over-all size of the heart is enlarged (Figs. 3 and 5).

The angiocardiograms in patients with a normal aortic root usually demonstrate earlier filling of the pulmonary artery and show a greater density of the contrast medium in the pulmonary artery than in the aorta (Fig. 6). Even when the flow through the ventricular shunt is right to left, the pulmonary artery fills with greater contrast than the aorta (Fig. 7). The aortic root is relatively comparable in size to its more distal portion and arch, in contrast to the marked discrepancy in size in patients with Fallot's tetralogy. The aorta in the lateral view is in its normal position, posterior to the pulmonary artery (Fig. 7). Often the pulmonary artery and its branches are unusually well developed. Left atrial enlargement can frequently be seen on the angiocardiogram (Fig. 8).

The finding of large diphasic complexes in the electrocardiogram often is one of the distinguishing features that separates the normal-root entity from Fallot's tetralogy (Fig. 9). In addition, although several patients presented the findings of isolated pulmonic stenosis, the electrocardiographic



Fig. 2. Tetralogy of Fallot in Patient D H. *Left:* Normal size of heart preoperatively. *Right.* Larger cardiac shadow 1 year postoperatively.



Fig. 3. *Above:* Over-all enlarged heart, hypervascular lungs, and large left atrium in Patient S G , 18 months old. *Below:* Normal lung fields, minimal enlargement of left atrium, and enlarged heart in same patient, 3½ years old; the changing conditions suggest progressive infundibular hypertrophy.

Table 1C. Tetralogy of Fallot

Name	*Age*	*Sex*	*Anatomic findings (surgical and/or postmortem evaluation)*	*Postoperative summary*
K.B.J	2	F	Pulmonary valve stenosed, bicuspid valve; large RV, RA enlarged, infundibulum narrowed, left ventricle normal size	Died postoperatively
D J.	28	F	Pulmonary valve stenosed, narrowed RV outflow, IVSD entered between infundibular mass and pulmonary valve	Postoperative cardiac failure. Huge heart. Residual IVSD repaired, with excellent clinical results, pulmonary insufficiency murmur. Pulmonary insufficiency proved by catheterization
C.S.	9	M	Pulmonary valve stenosed, muscular bands at RV outflow, 2 cm IVSD	Heart enlarged. Pulmonary insufficiency murmur. Acyanotic, well
J N	30	M	Pulmonary valve normal but artery small. Infundibulum hypertrophied, no LV hypertrophy. Heart weighed 480 Gm.	Died postoperatively
R C.	4	F	Pulmonary artery narrowed, hypertrophy of crista, right ventricle hypertrophied, and narrowed right ventricular outflow. LV not enlarged	Heart enlarged. Acyanotic, well
S S	16 mo	F	Pulmonary artery narrowed, fused leaflets, right ventricular outflow narrowed, left ventricle not enlarged	Died postoperatively
M S	3	F	Pulmonary valve leaflets normal but pulmonary artery and annulus narrowed, muscular bands at crista area, right ventricle enlarged, LV not enlarged	Heart enlarged. Acyanotic, well
M O	9	M	Pulmonary valve stenosed, fibrous bands below valve, diaphragm of muscle at RV outflow, pulmonary artery small, 1.5 cm. VSD	Heart enlarged. Acyanotic, well
J A	20	F	Pulmonary valve slightly stenosed, bicuspid valve, severe infundibular stenosis, marked dextroposition of aorta	Acyanotic, well
E F.	5	F	Pulmonary valve stenosed, fibrous obstruction of outflow of RV, pulmonary artery narrowed, right-sided aortic arch	Heart enlarged Murmur of pulmonary insufficiency. Acyanotic, well
D H	8	M	Pulmonary valve stenosed, infundibulum narrowed, small pulmonary artery	Heart enlarged, acyanotic, well, murmur of pulmonary insufficiency
R M	15 mo	M	Pulmonary valve stenosed, narrowed pulmonary artery, bicuspid pulmonary valve, infundibulum narrowed, RV enlarged, LA and LV normal. Heart weighed 65 Gm.	Died postoperatively
D E	40	M	Blalock procedure. RV enlarged	Cyanotic, clinically improved
C C	18 mo	M	Patent ductus arteriosus ligated, valvular pulmonic stenosis, moderate hypertrophied infundibular area, fibrotic bands at RV outflow tract, IVSD	No change in heart size, acyanotic, well
F.M.	7	M	Pulmonary valve normal, patent ductus arteriosus, infundibulum hypertrophied, IVSD	No change in heart size, residual VSD clinically, acyanotic
B.J.	8	M	Pulmonary valve normal, muscular bands at RV outflow tract, lungs congested, over-all size of heart enlarged (weighed 100 Gm.), RV and LV dilated, three defects in muscular ventricular septum	Died postoperatively

Murmurs	*ECG*	*X-ray films*
Grade 3 systolic, 4-ICS	RAD-RVH RAV_F = 30 mm.	Enlarged heart, clear lung fields, RA+−, LA+−, RV+, LV+
Grade 3 systolic, 2-3rd ICS	RAD-RVH-LVH	Enlarged heart, RA+, LA+
Grade 4 systolic, 3-LSE	RAD-RVH-LVH RAV_F = 25 mm.	Enlarged heart, concave PA—LA+, RV 2+
Grade 3 holosystolic-diastolic at apex	RAD-RVH-LVH	Normal-sized heart, RV−+, small aortic knob, normal lung fields
Grade 3 systolic, 2-4th ICS	RAD-RVH-LVH	Enlarged heart, lung fields clear, PA−+, LA−+, RV++, LV+
Grade 3 holosystolic	RAD-RVH	Enlarged heart, clear lung fields, concave PA segment, LA+, RV±
Ejection systolic 2nd ICS, holosystolic 3rd ICS	RAD-RVH-LVH	Enlarged heart, lung fields normal, RA+, LA+, RV++
Grade 3 holosystolic 2-3rd ICS suggestive of ejection component	RAD	1957 — enlarged heart, hypervascular lungs, LA 3+, RV+; 1959—enlarged heart, normal lung fields, concave PA-LA-O-RV+
Harsh systolic	RAD-RVH	1952—enlarged heart, prominence of PA, LV+, increased pulmonary vasculature
Holosystolic and ejection systolic	RVH—probably LVH	1959—enlarged heart, increased pulmonary vasculature, LA+, RV+
Holosystolic	RAD-RVH	Normal-sized heart, clear lung fields, RA+, RV+
Holosystolic, 3rd ICS	RAD, RAV_F 23.0 mm. RVH, suggestive of LVH	Lung fields normal, heart enlarged
Holosystolic, 4th LSE—harsher murmur at 2-3rd LSE	Age 6—RAD-RVH-LVH Age 9—RAD-RVH	Heart enlarged, RV+, lung fields clear to slightly hypervascular. Pulmonary artery segment +
Holosystolic	RVH-LVH	Heart enlarged, small aortic knob, LA+, LV+, RV+
Suggestion of harsh systolic as well as holosystolic	RAD-RVH-LVH	Heart enlarged, vascular markings normal Dilatation of pulmonary artery RV+, LV±, LA-0
Grade 3 harsh systolic pulmonary area	RAD-RVH	Normal sized heart, normal lung fields, RV+, aortic arch on right. Kyphoscoliosis
Harsh systolic, holosystolic in type with suggestion of ejection type in pulmonary area	RAD-RVH	Enlarged heart, RV+
Holosystolic and ejection systolic	RAD-RVH	Heart enlarged, hypervascular lung fields, RV+
Harsh holocystolic, 3rd ICS LSE	RAD-RVH-LVH	Clear lung fields, globular heart, RV+

of the related entity with normal aortic root. The partial transposition or override of the aorta, with persistence of the right ventricle as a systemic ventricle coexistent with the left ventricle, explains the dynamics of tetralogy of Fallot. The right ventricle communicates directly with the systemic circulation, and, therefore, is directly affected by the systemic resistance as well as the resistance to flow at its outflow tract or any changes that might take place in the underfilled pulmonary vasculature.[6,13,24,25] The left ventricle, therefore, never assumes its normal role and remains a relatively hypoplastic chamber or has a "petite volume" as described by Fallot. Tetralogy of Fallot is undoubtedly a single developmental anomaly, as emphasized by Spitzer[27] and corroborated by studies of Kramer,[25] and the greater the transposition, the greater is the severity the narrowing of the outflow tract

Table IIA. Pulmonic stenosis, ventricular septal defect with normal aortic root

Name	*Age*	*Sex*	*Cyanotic*	*Growth*	*Thrills*	*Sounds*
G L.	28 mo.	M	Yes	Normal	0	Diminished P_2
D.E.	4	F	0	Normal	Prominent left apex beat outside mid-clavicular line	$A_2 > P_2$
R B.	14	F	0	Normal	Systolic prominent left apex beat	Normally split $A_2 > P_2$
J B.	12	M	0	Normal	Systolic, 2–3rd LSE	Single 2nd
A J.	6	F	0	Mentally retarded	Systolic, 2–3rd LSE	Single 2nd
M L.M.	2½	F	0	Poor	Systolic, 3–4th LSE	P_2 diminished
C C.	17 mo	M	0	Normal	Systolic, 4th LSE	P_2 diminished, delayed
S G.	3½	F	0	Poor	Systolic, 2nd LSE	P_2 diminished, delayed
E B	12	M	0	Normal	Systolic, 2–3rd LSE	Murmur obliterated 2nd sounds
	19	M	0	Normal	Systolic, along LSE	P_2 diminished, delayed
N L	16	F	0	Normal	Systolic, 2–3rd ICS	Single 2nd
W F	12	M	Slightly	Normal	Systolic, 3rd ICS	Single 2nd
R C	9½	F	Syncope; Slightly	Poor	Systolic, 3–4th LSE	P_2 diminished
T D	6	M	0	Slightly slow	Systolic, 2nd LSE	P_2 normal
H A	8	M	0	Small	Widely distributed systolic	P_2 diminished
R K	52	M	0	Normal	0	P_2 diminished
V F	3½	M	Yes, clubbed	Normal	Systolic, 3–4th LSE	P_2 diminished, delayed
J B	4	M	At times	Small	3rd LSE	P_2 diminished, delayed
Y D.	6 mo.	F	Yes	Poor	3rd ICS, LSE	P_2 single

strated an interventricular septal defect, and in 3 other patients there is clinical evidence which strongly suggests a residual ventricular septal defect.[23]

Additional comment is indicated in W.F., whose right ventricular pressure exceeded systemic pressure by 88 mm. Hg at the time of cardiac catheterization and was confirmed with simultaneous pressure measurements at operation. The clinical evaluation, however, indicated a ventricular septal defect as well as pulmonic stenosis. At operation, a ventricular septal defect, 1.5 cm in diameter, just below the hypertrophied crista, was repaired.

Discussion

The distinction between the two groups of patients is physiological and developmental. The circulatory dynamics of the tetralogy of Fallot are distinct from those

Aorta		*Left ventricle*		*Pulmonary wedge (mean)*	*Angiocardiogram*
S/D	*Sat. (%)*	*S/D*	*Sat. (%)*		
					PA fills before aorta, aorta normal in *position and size*, right-to-left *shunt*, VSD seen
102/75	98	96/5			None
110/67	95				No premature opacification of aorta, left-to-right shunt seen, aorta *normal*, large LA on angiocardiogram
					Early simultaneous filling of aorta but not so intense as that of PA; aorta normal, infundibular and valvular pulmonic stenosis, right-to-left shunt demonstrated
					Early filling of PA not aorta. Aorta normal, IVSD demonstrated
					PA fills before aorta. Bidirectional shunt seen, pulmonary valve and infundibulum stenosed, normal aorta on cineangiocardiogram
					Aorta normal, no premature filling, stenosis of pulmonary valve and infundibulum
					Normal aorta, no premature filling, infundibular *stenosis*, right-to-left shunt seen
					Aorta does not fill prematurely, *normal* aorta, stenosis of pulmonary valve and infundibulum—age 19
			96		
					None
					Early filling of aorta, but not so dense as *that of* PA, and normal position, left-to-right shunt seen Venous angiocardiogram
				14	None
		109/2	98	12	
					None
				10	Pulmonic valvular stenosis, normal position and *size of aorta*
					PA fills before aorta, infundibular stenosis, bidirectional shunt, cineangiocardiogram
					Aorta normal in position and size, bidirectional shunt seen, pulmonary valves *normal*, infundibular stenosis
		96/10	73	LA 77 A = 11 V = 8	PA fills earlier than aorta Aorta normal in position and size. RV and LV enlarged Infundibular stenosis and bidirectional shunt; cineangiocardiogram

with a patent ductus arteriosus or right-to-left shunt at the atrial level,[30] then a more normal or even increased flow to the left ventricle will be expected (F.M. and C.C.). These patients, clinically and physiologically, should be indistinguishable from those with a normal aortic root. A patent ductus arteriosus associated with a Fallot heart should be readily discernible by the continuous murmur; however, a clinical diagnosis was not made in F.M. prior to operation. In 10 autopsied patients with tetralogy of Fallot reported on by Brinton and Campbell,[31] there was evidence of an atrial septal defect but no associated left ventricular hypertrophy. The findings in this report imply physiologically small shunts through the atrial septal defects. Therefore, one questions whether the enlarged left ventricle in a "pentalogy of Fallot" is really due to the associated atrial septal defect, or whether the total findings are not the result of a physiologically insignificant atrial septal

Table IIB. Pulmonic stenosis, ventricular septal defect with normal aortic root

Name	Age	Sex	SVC (% Sat.)	IVC (% Sat.)	Right atrium			Right ventricle		Pulmonary artery		Systemic artery	
					A	V	Sat. (%)	S/D	Sat. (%)	S/D	Sat. (%)	S/D	Sat. (%)
						Rate 120							
G.L.	28 mo.	M	45	53	10	4	47	92/0	53	11/4	55	73/40	72
D.E.	4	F	70	76	6	4	69	86/5	86	44/17		121/75 B	98
R.B	14	F	64		7	4	65	118/0	82	38/7	79	93/64	98
J.B.	10	M	71	67	20	10		115/0	67	NE		115/64	94
A.J.	6	F	69		9	8	69	128/10	75	55/21	82	121/71	80-98
M.L.M	2	F	74	78	7	3	73	88/0	75	OR 15/9		96/52	95
C.C.	17 mo.	M	75	79	9	5		98/0	84	NE		105/69	92
S.G	3½ (1959)	F	59	59	14	8	64	81/2	65	17/9	64	100/63	87-95
E.B	12	M	40				55	108/0	69	50/8	69	127/85	95
	19		65	71	10	5	72	107/0	84	19/9	84	105/60	99
T D	6	M	81	85	18	10	81	112/5	92.5	68/14	94	130/65	98
N L.	16	F	74	81		73		100/0	78	16/10	80	77/58	98
W F.	12	M						208/3		12/1		120/80	82
	6		72		6	4	68	55/13	67	28/12	73	104/57	93
R C	7	F	76	72	10	7	74	80/5	81	25/10	81	87/54	98
	9½		67	68	11	6		92/0	81	30/12	81	103/48 B	98
R K	32	M	53		8	3	53	102/1	74.5	15/5	76	110/60	94
H A	8	M	71	75	8	7	71	88/5	75	16/6	75	110/70	95
V T	3½	M	65		10	6	61	103/7	65	25/9	65	110/52	75-82
J B	4½	M	64	70	10	8	64	123/13	70	NE		133/75	81
Y D.	6 mo	F	63	67	10	5	65	100/8	65	NE			

B: Brachial arterial pressure. OR: Operating room pressure. For other abbreviations see footnotes to Table IB.

right ventricle and pulmonary artery. One concludes from the existing data that tetralogy of Fallot represents a variation in the spectrum of transposition and may represent persistence of a more primitive phylogenetic circulation.[22] The embryologic consideration in Fallot's tetralogy has been reviewed by Edwards and associates.[23]

A comparison of the normal fetal circulation and the in utero circulation of the Fallot heart is diagrammed by Taussig[14] and clearly demonstrates the lack of circulatory stress on this heart in utero. At birth the resistance to flow at the right ventricular outflow tract is unchanged. As in utero, the right ventricle continues to supply blood to the systemic circuit via the "right ventricular aortic path" (Spitzer). A Fallot heart is the same dynamically from its development to death and, in a way, really represents an extrauterine functioning of a fetal heart.

If the true Fallot heart is associated

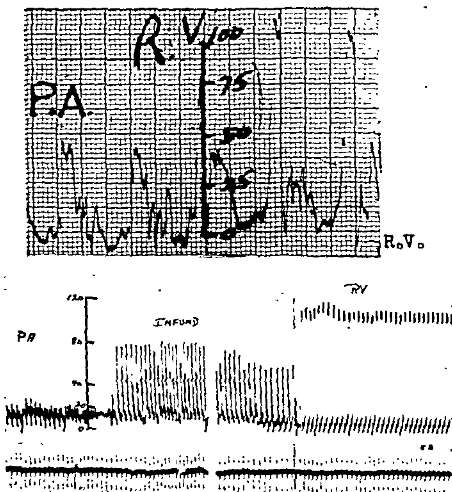


Fig. 4 *Above:* Patient E.B., 12 years old Pulmonary arterial and infundibular pressures are equal and above normal. *Below:* Same patient, 19 years old Distinct gradients at the pulmonary valve and infundibular chamber are noted; the pulmonary arterial pressure is normal.

defect in a pulmonic stenosis, ventricular septal defect with a normal aortic root.

It is important to note that the size of the heart in the 2 patients with patent ductus arteriosus (F.M. and C.C) did not increase postoperatively. This lack of change postoperatively may be due to the fact that the left ventricle was well developed previously because of an associated patent ductus arteriosus

The left ventricle of the in utero heart with ventricular septal defect and a nontransposed aorta may well be under increased work, since it contributes a greater share of blood to the systemic circulation because of the interventricular shunt (Fig. 12). However, Taussig[18] states the utero in heart with a ventricular septal defect is not under any stress. Shortly after birth the left ventricle continues to function as a high-output chamber, with the in utero right-to-left shunt reversed to left to right as the pulmonary resistance falls. If, in addition, severe pulmonic stenosis exists in utero, an even greater right-to-left shunt is present at the ventricular level. If the resistance at the outflow tract of the right ventricle is severe, then the flow of blood from left to right may never occur when the pulmonary resistance falls after birth. This hypothesis may help explain the findings in G.L. and Y.D., who were cyanotic from birth and yet had definite left ventricular hy-

Table IIC. Pulmonic stenosis, ventricular septal defect with normal aortic root

Name	*Age*	*Sex*	*Anatomic findings (surgical and/or postmortem evaluation)*	*Postoperative summary*
G L	2	M	Pulmonary valve deformed Infundibular stenosis Right and left ventricular hypertrophy and dilatation, heart enlarged, weighed 160 Gm.	Died postoperatively
D.E	4	F	Pulmonary valve stenosed, infundibular muscular hypertrophy, 3 cm high VSD—over-all size of heart enlarged	Clinically well, pulmonary insufficiency and residual VSD proved by catheterization, heart size unchanged, VSD closed at second open-heart operation
R.B.	14	F	*Pulmonary valve normal, 1 5 cm VSD—infundibular muscular hypertrophy*	Residual VSD—clinical evaluation, heart size unchanged
J.B	12	M	Pulmonary valve normal, infundibular muscular hypertrophy, 1 5 cm VSD, RA and RV enlarged, LV and LA appeared normal	Residual VSD, clinical evaluation
M L M	2½	F	Pulmonary valve deformed and stenosed, muscular hypertrophy of infundibulum, right and left ventricular hypertrophy, heart enlarged, intact bundle of His, heart weighed 100 Gm	Heart block, died postoperatively
A J	6	F	Pulmonary valves normal Second set of rudimentary pulmonary valves below normal set, 2 cm defect under aortic valve, fibrous and muscular hypertrophy of infundibular area, right and left ventricular hypertrophy, heart enlarged (weighed 150 Gm)	Died postoperatively
S G	3½	F	Pulmonary valves normal, muscular hypertrophy of infundibulum	No change in heart size, acyanotic, VSD, patient clinically well
W F	12	M	Pulmonary valve normal, infundibular muscular hypertrophy and IVSD	Residual VSD proved by catheterization
R C	9½	F	Bicuspid pulmonary valve stenosed Muscular hypertrophy of infundibulum, large high IVSD	Well, diastolic murmur in pulmonary area
T D	6	M	Pulmonary valves normal, large heart, muscular hypertrophy of infundibular area	Complicated by aortic insufficiency, repaired; doing well, VSD closed as proved by catheterization
N L	16	F	Pulmonary valve normal Infundibular stenosis with 1 5 cm VSD	Doing well
H A	8	M	Valvular pulmonic stenosis, 3-4 cm IVSD	Doing well
J B	4½	M	Pulmonary valve slightly thickened Infundibular hypertrophy, large heart and marked hypertrophy of right ventricle and ± hypertrophy left ventricle. Large LA and RA. Suggestive narrowing of pulmonary artery ring (weighed 80 Gm)	Died postoperatively, heart block
C C	27 mo	M	Pulmonary valvular stenosis. Large heart. No infundibular narrowing, large IVSD	Died at operation, no autopsy performed
Y D.	6 mo	F	Pulmonary valve normal Infundibular hypertrophy Hypertrophied left ventricle and right ventricle Right ventricular cavity very small. Patent foramen ovale	Died postoperatively

associated with incomplete transposition of the aorta and persistence of a right ventricular aortic flow; therefore, this entity should be considered within the spectrum of the transpositions. The second group, whether in utero development of pulmonic stenosis with interventricular septal defect or postnatal hypertrophy of the right ventricular outflow tract with interventricular septal defect, has evidence of a hyperdynamic left ventricle. It is the physiologic role of the left ventricle that separates these patients into two distinct groups.

We should like to thank Dr. F Claps, of the Cardiovascular Service, Lenox Hill Hospital, for allowing us to use the cardiac catheterization data and the angiocardiograms on Patient W F, and The Johns Hopkins Hospital for the data on Patient N.L.

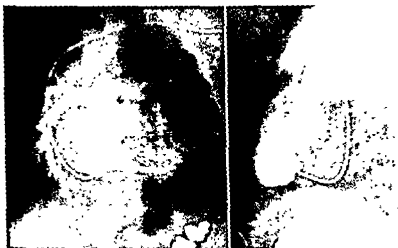


Fig. 7. The pulmonary arteries are well developed and fill earlier and with greater contrast than the aorta In the left lateral view the aorta is in normal position, and there is only minimal difference between the size of the base of the aorta and the size of the arch (Patient G L)



Fig 8. Large left atrium on angiocardiogram, the aortic root is comparable in size to the rest of the aorta (Patient S G)

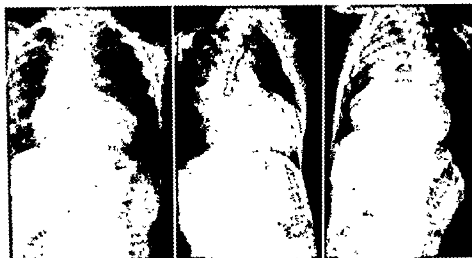


Fig. 5. The lung fields are hypovascular, with over-all enlargement of the heart. The right anterior oblique view suggests minimal enlargement of the left atrium. The left anterior oblique view strongly suggests an enlarged left as well as right ventricle in a cyanotic patient (G. L.) with normal aortic root.



Fig. 6. The pulmonary artery is well developed and fills 5/6 of a second before the aorta, (left view compared with right), the aorta has normal position and size (Patient S. G.). Compare with Fig. 1,A and B.

trophy when examined post mortem. It is this hyperdynamic chamber which manifests itself in the clinical and laboratory findings outlined and allows for its differentiation from Fallot's tetralogy.

Those patients who initially had a ventricular septal defect and developed progressive infundibular hypertrophy, to the point of an absence of a left-to-right shunt at the ventricular level, still revealed some evidence of a well-developed left ventricle, which, therefore, indicated a normal aortic root. We believe that many of the reported cases of atypical tetralogy of Fallot fall into our classification of pulmonic stenosis, ventricular septal defect with normal aortic root.[32-40]

Summary

A physiologic and clinical approach has been employed to distinguish two groups of patients who were anatomically similar: one group had pulmonic stenosis, ventricular septal defect with overriding aorta (tetralogy of Fallot); and the second group had pulmonic stenosis, ventricular septal defect with normal aortic root. The former group has a single developmental defect

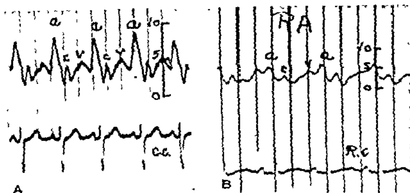


Fig. 11. A, Right atrial tracings which demonstrate dominant A waves (Patient C.C.). B, Normal right atrial tracing in a case of Fallot's tetralogy (Patient R.C.).

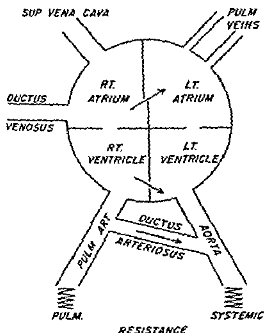


Fig. 12. In utero circulation in a case of ventricular septal defect, postulating increased work load on the left ventricle.

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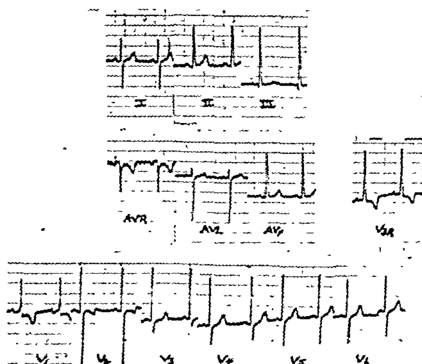


Fig. 9 Electrocardiogram of Patient N.L. Right axis deviation and right ventricular hypertrophy. Note progressive increase in the R wave in Leads V_2-V_5 and the deep S wave Lead V_2

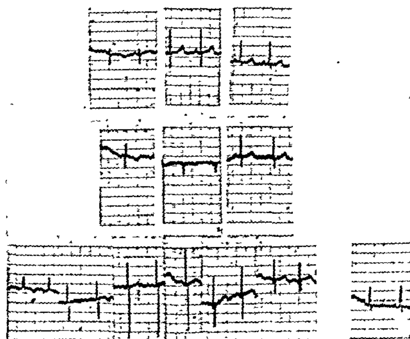


Fig. 10. Electrocardiogram of Patient H.A. Right axis deviation and right ventricular hypertrophy, and large S waves in Leads V_3, V_4, and increasing R waves in Leads V_2 to V_4.

Splitting of the second heart sound in constrictive pericarditis, with observations on the mechanism of pulsus paradoxus

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For some years we have been aware of a peculiar type of splitting of the second heart sound in constrictive pericarditis associated with a well-marked pulsus paradoxus. The findings are so distinctive that constrictive pericarditis has often been suggested on auscultation even in patients without the characteristic third heart sound. The unusual feature has been the abrupt and short-lived widening at the onset of inspiration. Its mechanism, however, was not realized until analysis of phonocardiographic recordings showed that the inspiratory widening of the split second sound was almost entirely due to movement of the aortic component.

Since the movement of the aortic component of the second sound appeared to be related to the shortening of left ventricular systole and the small arterial pulse during inspiration, additional studies were performed in 3 patients in an attempt to elucidate the mechanism of the reduced inspiratory left ventricular output in constrictive pericarditis.

Material and methods

Four patients with classic constrictive pericarditis were studied phonocardiographically; in 3 of these the diagnosis was subsequently proved by operation. Simultaneous tracings of heart sounds, the electrocardiogram, and the external carotid or brachial pulses were recorded on a 6-channel N E P. recorder. Synchronous phonocardiographic tracings were recorded at the pulmonary area and the fourth left intercostal space, or the mitral area.

Tracings were obtained during normal quiet respiration and during deep exaggerated respiration. The phases of respiration were signaled on the record by the investigator. The onset of inspiration could be confirmed by the respiratory murmur in some of the phonocardiographic tracings.

The aortic component of the second sound was identified by its relation to the dicrotic notch of the carotid pulse, or by the fact that it was the loudest or only component recorded at the mitral area.[1] The R wave of the electrocardiogram and the peak vibrations of the sounds were used to record the R-A_2 and R-P_2 intervals in this study, since these gave the most accurate and easily identifiable measuring points.[2]

Records were taken at paper speeds of

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patients the effects of a prolonged inspiration, i.e., continued inspiratory effort with open glottis, was also noted.

In one patient (Patient 4) a direct left atrial puncture was performed, using a Ross transseptal needle inserted percutaneously via the right femoral vein. Simultaneous wedge and direct left atrial pressures were then recorded, during normal and exaggerated respiration and prolonged inspiration.

Results

The *phonocardiographic* results are shown in graphic form in the 4 subjects (Fig. 1). During normal respiration there was very little respiratory sinus arrhythmia, as shown by the almost constant R-R interval. The A_2-P_2 interval during expiration varied between 0.01 and 0.04 second. During the first heartbeat after the onset of inspiration the split abruptly increased by 0.03 second in all cases. In Patient 1, movement of P_2 contributed nothing to the increase in the split, whereas in the other 3 patients, P_2 moved only 0.01 second from the R wave. Thus, most of the widening was due to shortening of the R-A_2 interval. The small arterial pulse occurred at the time of the wide split, associated with the abrupt shortening of the R-A_2 interval (Fig. 2).

During exaggerated respiration the R-R interval fluctuated, because of respiratory sinus arrhythmia, but the maximal movements of A_2 and P_2 were of the same magnitude as in quiet respiration (Fig. 1).

During the succeeding inspiratory beats the R-A_2 interval began to return to its expiratory position, so that the maximal movement of A_2 and the widest split occurred during the first beat after the onset of inspiration. The external pulse records, which reflect qualitative changes in pressure,[4] also showed that there was close correlation between the arterial pressure pulse and the width of the split, i.e., the maximum fall in arterial pressure pulse occurred one beat after the onset of inspiration, at the time of maximal shortening of the R-A_2 interval. Thereafter, as the R-A_2 interval increased, so the arterial pressure pulse increased (Fig. 3).

Catheterization data. The data obtained by routine catheterization of the right side of the heart in Patients 2, 3, and 4 are shown in Table I. All showed the classic features of constrictive pericarditis—the elevated right atrial pressure with rapid x and y descents, the right ventricular early diastolic dip, the rapid upstroke of the large stasis wave, and the high end-diastolic right ventricular pressure. The wedge and direct left atrial pressures were elevated to levels similar to those found in the right atrium. Cardiac output was low in Patients 3 and 4, but normal in Patient 2.

Respiratory fluctuations. During quiet, normal respiration, right atrial pressure showed no fluctuations in Patient 2 (Fig. 4,*A*), and a slight initial fall in Patients 3 and 4 (Fig. 4,*B* and *C*). On the other hand, the wedge pressure fell at the onset of inspiration; the fall was similar in magnitude to that found in normal subjects.[5] The simultaneously recorded systemic pressure pulses showed that the fall in systemic and pulse pressure occurred one beat after the sharp fall in wedge pressure, and remained small for one or two beats only (Fig. 4). Tracings taken at paper speeds of 75 to 80 mm. per second confirmed the relationship between small pulse and short R-A_2 interval. The smallest arterial pulse and the widest

Table I. Pressures (in mm. Hg)

Patient	Right atrium	Right ventricle	Pulmonary artery	Mean	Pulmonary capillary	Mean	Cardiac output (L./min.)	Index (L./min./M.²)	Arteriovenous O_2 difference (ml/L.)
2.	24/18	43/18-24	38/22	29	26/21	22	8	7.5	31.5
3	22/15	32/15-22	30/25	26	24/20	21	3 2	2.0	56.5
4.	18/11	33/11-18	34/24	26	25/20	22	2 4	2.1	50

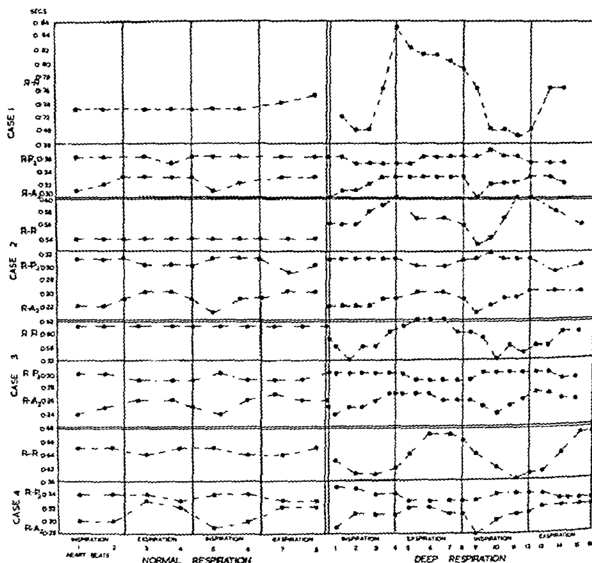


Fig. 1. The time intervals between the R wave of the ECG and A_2 and P_2, as well as the R-R interval in the 4 patients studied, are shown. The time intervals in seconds are plotted along the ordinate, and each heartbeat along the abscissa, the vertical lines divide inspiration from expiration. The columns on the left show the movement of A_2 during normal quiet inspiration, and those on the right, during deep exaggerated respiration. The R-R interval is constant during quiet respiration but varies, because of respiratory sinus arrhythmia, during deep respiration.

75 to 80 mm. per second, and the measurements were made to the nearest 0.01 of a second. The R-A_2 and R-P_2 intervals, together with the R-R intervals, were recorded during two consecutive respiratory cycles during both normal and exaggerated respiration.

In 3 patients (Patients 2, 3, and 4), routine catheterizations of the right side of the heart were performed as previously described.[3] The zero reference point was taken at mid-chest level. A second venous catheter was inserted into the right atrium; the first was wedged into the pulmonary artery to record a pulmonary arterial wedge pressure. Systemic pressure was recorded via a needle in the radial or brachial artery. Simultaneous right atrial, wedge, and systemic pressures were recorded at slow (8 to 25 mm. per second) and fast speeds, together with the electrocardiogram and external phonocardiogram at the pulmonary and mitral areas, during normal and exaggerated respiration. In 2

of the second sound and the small arterial pulse by one beat. Thereafter, in spite of continuing inspiration, the wedge pressure began to rise, splitting narrowed, and the arterial pressure climbed. This pattern was seen with each respiratory cycle.

A prolonged inspiration in Patient 2 (Fig. 7,*A*) initially produced the usual fall in wedge pressure and systemic pressure and no change in the right atrial pressure, but after one beat, both right atrial and wedge pressure rose considerably and remained elevated for the duration of the inspiration. It is noteworthy that after the transient fall the systemic pressure rose rapidly and was well maintained. Moreover, the rise in wedge pressure followed the inspiratory fall in systemic pressure. In Patient 4 (Fig. 7,*B*) there was a slight drop in all three pressures which persisted for the duration of the inspiration, without any rise in right atrial and wedge pressures.

In Patient 4 (Fig. 8,*A*), when simultaneous wedge and direct left atrial pressures were measured, wedge pressure exceeded direct atrial pressure by about 4 mm. Hg during expiration (Table II). Although the two pressures showed similar respiratory fluctuation during both normal and exaggerated expiration, the wedge pressure fluctuated to a greater extent, so that during inspiration the gradient between wedge and left atrium was reduced from 4 to 2 mm. Hg (Table II).

In summary, therefore, the following facts emerge. During normal inspiration the wide splitting of the second sound is predominantly due to an abnormal shortening of the R-A_2 interval and relative fixity of the R-P_2 interval and is related in time and magnitude to the smallness of the arterial pulse. During deep inspiration these events are maximal at the onset of inspiration, occur one beat after the normal inspiratory drop in wedge pressure, and recover rapidly with each succeeding beat. Right atrial pressures show far less respiratory fluctuation.

In one patient, during a prolonged inspiration with open glottis, the wedge and right atrial pressures both rose considerably a few beats after the onset of inspiration and remained elevated until

Table II

Patient and site	Normal respiration		Exaggerated respiration				Prolonged inspiration			
			Inspiration		Expiration		Inspiration		Expiration	
	Inspiration	Expiration	Early	Late	Early	Late	Early	Late	Early	Late
2. Right atrium	23/17	24/18	25/20	28/24	24/17	23/17	23/17	28/21	23/18	24/17
Right pulmonary artery wedge	27/22	31/26	21/17	40/31	35/28	30/23	21/17	42/33	35/28	30/24
Right brachial artery	112/83	118/85	100/72	112/80	117/82	112/77	100/75	110/80	112/80	110/82
3. Right atrium	21/14	23/15	19/14	21/14	24/16	23/16				
Left pulmonary artery wedge	19/17	25/22	15/19	21/19	26/24	22/21				
Right radial artery	89/65	100/68	67/48	80/52	93/60	85/55				
4. Right atrium	17/10	18/11	17/11	18/10	18/11	18/11	15/9	16/8	18/10	18/10
Right pulmonary artery wedge	21/17	27/21	18/14	20/16	25/21	22/19	17/13	22/16	27/20	23/17
Left atrium	20/13	22/15	18/11	19/13	23/15	22/15	15/10	18/11	21/13	19/12
Right femoral artery	92/65	99/68	92/68	98/68	102/72	100/70	85/60	92/57	97/57	87/52

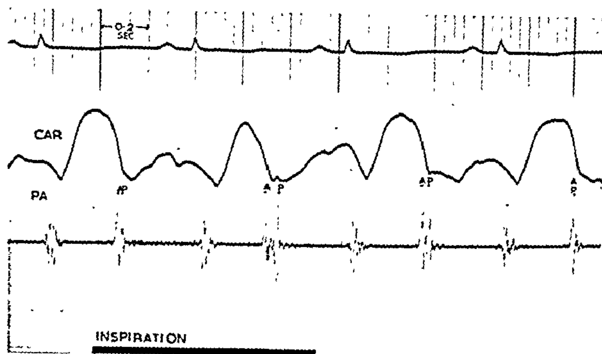


Fig. 2. The simultaneously recorded electrocardiogram, external carotid pulse, and phonocardiogram at the pulmonary area from Patient 4, during normal respiration. During expiration, A_2 and P_2 are separated by no more than 0.02 second. During the first heartbeat after the onset of inspiration the split widens to 0.06 second, chiefly because of shortening of the R-A_2 interval. This shortened left ventricular ejection time corresponds to the small external carotid pulse.

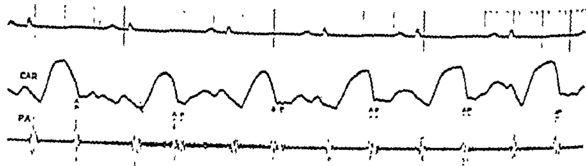


Fig. 3. The electrocardiogram, carotid pulse tracing, and pulmonary area phonocardiogram during deep exaggerated respiration from Patient 4. The split widens dramatically at the onset of inspiration, predominantly because of a leftward movement of A_2, and thereafter gradually narrows, although the inspiratory effort is continued. The smallest carotid pulse occurs with the widest split, and, as the split narrows, so the pulse increases in amplitude.

split occurred one beat after the sharp fall in wedge pressure (Fig. 5,*A*).

Tracings taken at slow speeds during exaggerated respiration showed greater fluctuations of wedge and systemic pressures. By contrast, the respiratory fluctuations in right atrial pressure were very modest, increasing only slightly in Patients 3 and 4 (Fig. 6,*A* and *B*). In Patient 2 (Fig. 6,*C*), right atrial pressure actually rose during a deep inspiration. Tracings at fast speed (Fig. 5,*B*) showed that the initial fall in wedge pressure, at the onset of inspiration, preceded the wide splitting

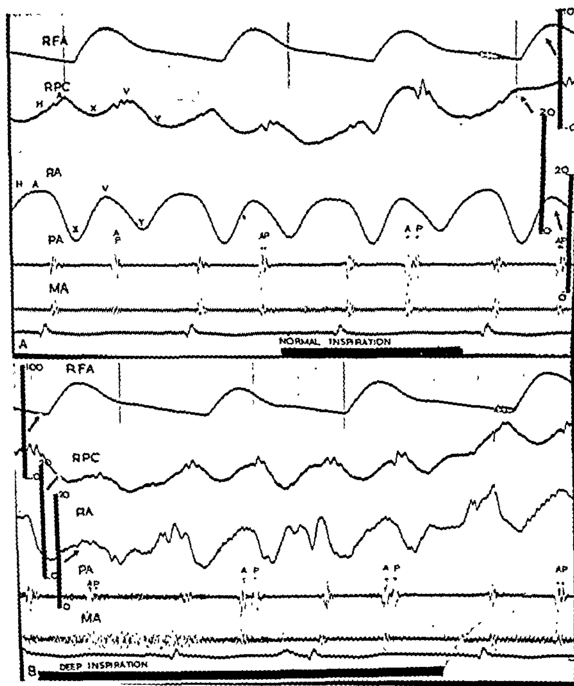


Fig. 5 The same tracings as in Fig. 4, taken at paper speeds of 75 to 80 mm. per second from Patient 4 during normal (*A*) and deep respiration (*B*). In both instances the fall in wedge pressure precedes the abbreviated left ventricular systole by one beat. In *B*, in the later phase of inspiration, wedge and systemic pressures begin to rise and the split narrows.

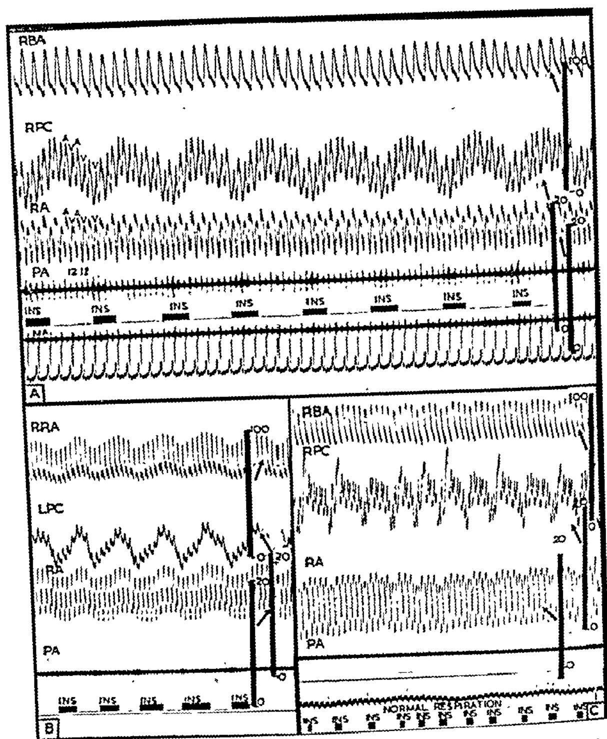


Fig. 4. The simultaneously recorded arterial, wedge, and right atrial pressures, pulmonary area phonocardiograms, and electrocardiograms from Patients 2 (*A*), 3 (*B*), and 4 (*C*) during normal respiration. The wedge tracing in *B* is severely damped. Systemic pressure shows an inspiratory fall, but only in Patient 3 is it of sufficient magnitude to be called a pulsus paradoxus. The wedge pressure shows the usual normal respiratory fluctuation. The drop in systemic pressure occurs one beat after the sharp initial fall in wedge pressure. Right atrial pressure falls by only 1 to 2 mm. during inspiration.

tinued. Elevation of atrial pressures during inspiration was, therefore, not invariable, and, when present, it followed the drop in arterial pressure and the shortened left ventricular systole.

A small pressure gradient could be demonstrated between the pulmonary veins and the left atrium during both phases of respiration in the one patient in whom this was measured. However, left atrial pressure fluctuated less than the wedge pressure, so that the gradient between the pulmonary veins and the left atrium appeared to be lower at the onset of inspiration than during expiration.

Discussion

Splitting of the second heart sound is due to asynchronous closure of the aortic and pulmonary valves. In health, during expiration the pulmonary and aortic components are synchronous, or else the pulmonary follows the aortic by no more than 0.04 second. During inspiration the split widens up to as much as 0.1 second.[6] Earlier investigations attributed this to a movement of P_2 away from the aortic component.[6] Recently, it has been emphasized that at least 18 to 50 per cent of the increased width of splitting during inspiration is due to a movement of A_2 toward the first sound.[3,7-9]

The time interval between the first and second sounds, or the R wave of the electrocardiogram and the second sound, is related to the duration of ventricular systole, and, in the presence of a constant heart rate, changes in the duration of systole are due to changes in ventricular stroke volume.[10,11]

It has been shown that during both normal and deep inspiration there is a drop in right atrial pressure,[12] an increased gradient between extrathoracic and intrathoracic vessels,[12] an increased inflow into the venae cavae and right atrium,[13] an increased effective right atrial pressure,[12] an increased end-diastolic volume in the right ventricle,[14] an increased right ventricular stroke volume,[15] and a prolongation of right ventricular ejection time. Hence, the R-P_2 interval is increased.

The effects of inspiration on the pulmonary vascular resistance and capacity has been much disputed. Critical analysis of the evidence appears to support the contention that pulmonary capacity increases[16] and resistance decreases.[17] This increased capacity exceeds the increase in right ventricular outflow, so that the blood tends to pool in the lungs. Thus, there is a decreased effective left atrial pressure,[12] a decreased left ventricular stroke volume and ejection time, a shortening of the R-A_2 interval and a slight fall in systemic pressure. The fall in systemic pressure may be due in part to the increased inspiratory capacity of the intrathoracic aorta,[18] but is due chiefly to reduced left ventricular output.[15,19]

During expiration these changes are reversed. Right ventricular stroke volume falls and left ventricular output increases, so that A_2 and P_2 come closer together or are superimposed. Normally, the effects of respiration are greater on the right ventricle than on the left, probably because of the greater distensibility of the right ventricle[20] and the buffering action of the intervening pulmonary blood volume.[16] Hence, the respiratory movement of P_2 normally exceeds that of A_2.[8,9]

To the best of our knowledge, inspiratory widening of the split second sound in constrictive pericarditis has not previously been recognized to be abnormal, although published records of heart sounds during inspiration and expiration have shown the abnormal shortening of the R-A_2 interval.[21] (Fig. 7) Wood[22] stated that one would not expect to find normal inspiratory widening of the split since the constricted right ventricle cannot respond to the augmented venous inflow. In fact, the pulmonary component does move very little or not at all, but the split widens dramatically because of the abrupt movement of A_2 toward the R wave of the electrocardiogram.

Premature closure of the aortic valve as a cause of unduly wide splitting has been well documented in mitral incompetence[23,24] and in left atrial myxoma,[25] and has been attributed to a reduction in the amount of blood ejected into the aorta in these conditions. Weissler and associates[11] have shown that the duration of left ventricular systole as measured from the carotid pulse wave is r[illegible]

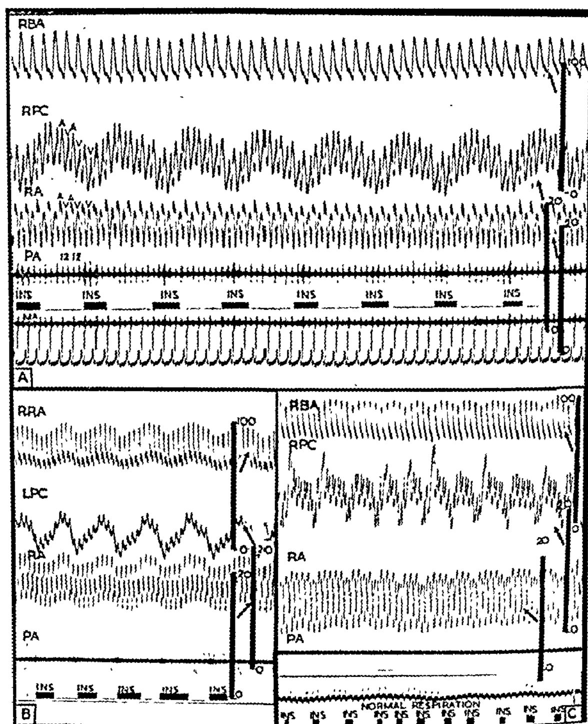


Fig. 4. The simultaneously recorded arterial, wedge, and right atrial pressures, pulmonary area phonocardiograms, and electrocardiograms from Patients 2 (*A*), 3 (*B*), and 4 (*C*) during normal respiration. The wedge tracing in *B* is severely damped. Systemic pressure shows an inspiratory fall, but only in Patient 3 is it of sufficient magnitude to be called a pulsus paradoxus. The wedge pressure shows the usual normal respiratory fluctuation. The drop in systemic pressure occurs one beat after the sharp initial fall in wedge pressure. Right atrial pressure falls by only 1 to 2 mm. during inspiration.

pericarditis; they attributed this to the reduction in left ventricular stroke volume.

The present study, as well as the studies of numerous other investigators, are in agreement that the phenomenon of pulsus paradoxus is due to an abnormal reduction in inspiratory left ventricular stroke volume. The abnormal behavior of the aortic and pulmonary components of the second sound in constrictive pericarditis during inspiration can thus be attributed to the unvarying right ventricular, and the reduced left ventricular stroke volumes, the latter being directly related to the phenomenon of pulsus paradoxus.

Controversy in regard to the mechanism of pulsus paradoxus has raged for years. All recent views recognize interference with diastolic filling of the left ventricle during inspiration as the basic cause of this phenomenon. Older views expressed by Kussmaul and Wenckebach and many others have been well reviewed by Gauchat and Katz,[26] and the more recent ones by McKusick and Harvey.[27]

There appear to be at least four separate views based on physiologic principles. Katz and Gauchat[28] studied cardiac tamponade experimentally in dogs, and were able to show that pulsus paradoxus was dependent on fluctuations in intrathoracic pressure during respiration. By successively occluding the aorta, the pulmonary veins, and superior vena cava, and measuring the number of heartbeats which elapsed before the systemic pressure fell, they were able to localize the hold up of blood to the level of the pulmonary veins. They expressed the view that during inspiration the extrapericardial vessels were more affected by the increased negative intrapleural pressure than were those within the pericardium, so that a temporary diminution, or obliteration, or even reversal of normal pressure gradient between the pulmonary veins and the left side of the heart would occur. This leads to underfilling of the left ventricle and the production of the paradoxical pulse. They could not measure these pressure gradients on the left side, but on the right side they were able to show a slight fall of about 2 mm. Hg in the pressure gradient between extrapericardial intrathoracic veins and the right atrium, during inspiration.

More recently, Sharp and associates[29]

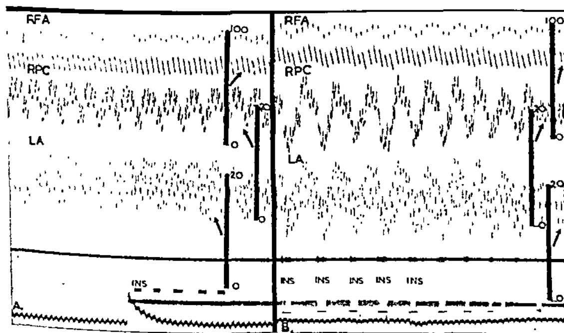


Fig. 8. The simultaneously recorded systemic, wedge, and left atrial pressures in Patient 4 during normal (*A*) and deep (*B*) respiration. In both cases, wedge pressure fluctuates more than does left atrial pressure, so that the small expiratory gradient of 2 to 4 mm. Hg between wedge and left atrium during expirat[illegible] to 1 or 2 mm. during inspiration.

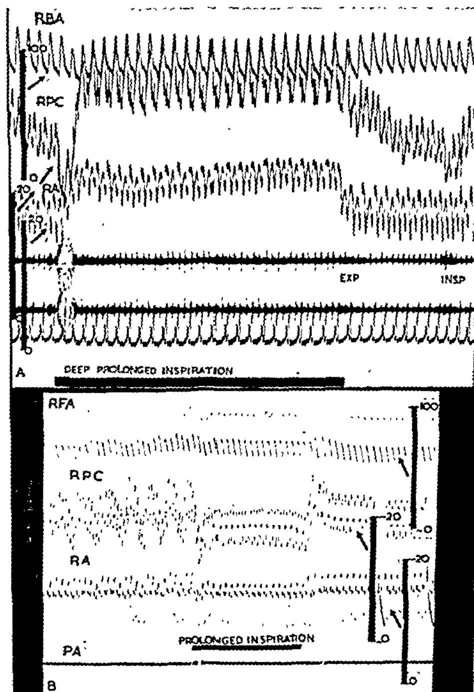


Fig. 7. Systemic, wedge and right atrial pressures during a prolonged inspiration in Patients 2 (*A*) and 4 (*B*). In *A*, after the initial inspiratory fall in wedge pressure, both wedge and right atrial pressures rise considerably. The drop in systemic pressure, however, follows one beat after the initial fall in wedge pressure and is not related to the subsequent rise. In Patient 4 (*B*) a prolonged inspiration produced no rise in wedge or right atrial pressure, and these pressures remain at their average inspiratory level. The usual short-lived fall in systemic pressure occurs at the onset of inspiration, together with the sharp initial inspiratory fall in wedge pressure.

tend more than intrapericardial structures, with an obliteration or reversal of the normal pulmonary venous-left atrial pressure gradient. There will be a greater than normal tendency for blood to pool in the pulmonary veins, with consequent exaggerated underfilling of the left heart.

On the right side, in addition to the elevated venous pressure a very large venous reservoir is present throughout the respiratory cycle. Thus, even if the gradient between the extrapericardial and intrapericardial structures were to become reduced, as on the left side of the heart, right ventricular underfilling would not occur. Because of the altered pressure-volume relationship of the right ventricle, the relatively large increase in right atrial pressure, which is found in some cases, remains ineffective in increasing ventricular filling. Hence, the right ventricular output tends to be fixed.

In conclusion, therefore, our phonocardiographic studies confirm that during the respiratory cycle in subjects with constrictive pericarditis the right ventricular output is fixed, whereas the left ventricular stroke volume shows an abrupt diminution at the onset of inspiration. Our catheter study in Patient 4 supports the findings of Katz and Gauchat,[28] Sharp and associates,[29] and Golinko and associates,[30] in that the left atrial pressure was found to fluctuate less than the pulmonary venous pressure, so that during inspiration the pressure gradient between the pulmonary veins and the left atrium was less than during expiration. Our data have also shown that wedge pressures may rise during the later phase of inspiration, but that this phase is not related in time to the drop in systemic pressure.

Summary

An unusual form of inspiratory widening of the split second sound is reported in 4 cases of constrictive pericarditis with pulsus paradoxus. The widened split is due to a sharp initial movement of A_2 toward the R wave of the electrocardiogram while the R-P_2 interval remains relatively fixed.

Clinically, the split appears to be unusual in that it occurs right at the onset of inspiration and lasts for one or two beats only, but it is only by phonocardiography that the predominant movement of A_2 can be established.

The shortening of the R-A_2 interval during inspiration is related in time of onset and magnitude to the drop in systemic pressure: both events are attributed to a reduction in left ventricular stroke volume.

Catheter studies in 3 patients showed that both the wide split and the small arterial pulse occurred one beat after a sharp fall in wedge pressure and were not related to the subsequent rise in wedge pressure that occurred during a prolonged inspiration in one patient.

Right atrial pressures showed minimal respiratory fluctuations. Simultaneous wedge and left atrial tracings in one patient showed a diminution in pressure gradient between wedge and left atrium during inspiration. This confirms previous work that pulsus paradoxus occurs as a result of differential effects of the negative intrathoracic pressure on intrapericardial and extrapericardial structures.

The relatively late rise in right atrial and wedge pressures that occurs during inspiration in some cases may be due to increased intrapericardial tension produced by diaphragmatic descent but is unrelated to the fundamental mechanism of pulsus paradoxus.

We wish to thank Dr. C. Rainser-Pope for his assistance with the cardiac catheterizations and the Superintendent, Dr. J. G. Burger, for his permission to publish. We gratefully acknowledge the technical assistance from our chief technician, Mr. L. W. Piller, his assistants, and the nursing staff. We are particularly grateful to the Council for Scientific and Industrial Research and the City Council of Cape Town for their continued support.

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studied the paradoxical pulse and were able to show that during inspiration the intrapericardial pressure fell less than did the wedge pressure. This suggests that a reduction in gradient between pulmonary veins and intrapericardial structures does in fact occur. Similarly, Golinko and associates,[20] studying induced tamponade in dogs, showed that pulmonary venous pressure exhibited greater respiratory fluctuations than did left atrial pressure, supporting Katz and Gauchat's view. The only objection to the latter's suggestion has been that it does not account for the situation in which the atrial and venous pressures rise during inspiration. This phenomenon, however, is not invariable in the pericardial syndrome, and it weakens but does not disprove their hypothesis.

Hitzig[21] studied the phenomenon of the inspiratory rise in cervical venous pressure that occurs in some cases of the pericardial syndrome. He suggested that the rise in cervical venous pressure and the pulsus paradoxus were hemodynamically independent phenomena. The former event was attributable to inability of the compressed ventricle to respond to the normal inspiratory influx of blood, and the latter to chronic underfilling of the lungs, so that the normal inspiratory increase in pulmonary vascular capacity caused a disproportionate fall in left ventricular filling pressure and the phenomenon of pulsus paradoxus. In our opinion, this hypothesis is unlikely since chronic pulmonary vascular underfilling does not invariably occur in the pericardial syndrome. In fact, acute pulmonary congestion and edema together with a paradoxical pulse is known to occur in constrictive pericarditis (personal observations). Since the respiratory fluctuations in the wedge pressures did not exceed normal limits in our cases, it cannot be argued that failure of the right ventricle to increase its output normally during inspiration causes a disproportion between the inspiratory vascular capacity and the amount of blood in the pulmonary circuit.

Dornhorst and associates[22] suggested that the occurrence of an inspiratory increase in right ventricular volume in an indistensible pericardial sac left proportionately less room for left ventricular filling, and, hence, the paradoxical pulse. Our observations on the fixity of the R-P_2 interval suggest that the right ventricle does not increase its end-diastolic volume much during inspiration, and, hence, this hypothesis is unlikely.

Lower, in 1669,[23] was probably the first to suggest that diaphragmatic descent during inspiration impeded the movements of the heart, leading to a small pulse. In 1956 and again in 1961, Wood[22,24] observed that during a prolonged inspiration, both wedge and right atrial pressures increased, and concluded that descent of the diaphragm stretched an already tense pericardium, leading to impaired ventricular filling, a reduction in left ventricular stroke volume, and a small arterial pulse. He was thus able to explain the rise in venous pressure and the fall in systemic pressure on the basis of the same mechanism. This view has recently been championed by Dock,[25] who showed that in cadavers the elevation of the sternum and the descent of the diaphragm elevated intrapericardial pressure when the sac was distended with fluid.

Only one of our 3 patients showed a rise in wedge pressure during inspiration, and this followed the initial fall. However, simultaneous systemic arterial tracings clearly showed that the fall in systemic pressure occurred one beat after wedge pressure had fallen and not during the subsequent rise. Thus, the rise in left ventricular filling pressure is neither invariable nor, when it does occur, is it related in time to the drop in arterial pressure. It follows that increased intrapericardial tension during inspiration may well account for the rise in pulmonary venous pressure when it does occur, but cannot be the mechanism by which the paradoxical pulse is produced.

The basic hemodynamic abnormality in the pericardial syndrome has been shown to be the relative indistensibility of the intrapericardial structures.[26,27] This leads to an altered pressure-volume relationship of the constricted atria and ventricles. On theoretical grounds, therefore, if the extrapericardial pulmonary vessels are normally distensible but the intrapericardial structures cannot distend, then, during inspiration, extrapericardial veins will dis-

Experimental and laboratory reports

Assisted circulation. II. The effect of heart rate on synchronized arterial counterpulsation

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This series of communications is addressed to the study of extracorporeal assistance for circulatory and myocardial insufficiency.[1,2] Such a technique may be lifesaving during the acute stage of myocardial infarction which is not responsive to medical measures. Patients suffering myocardial failure from any cause should be benefited if the myocardial work and oxygen requirements are reduced while the systemic and coronary circulations are supported until the heart regains its ability to perform pressure work.

Studies by Sarnoff and his collaborators[3] and by Katz[4] demonstrate the dominant role of pressure work, specifically systolic pressure, in determining myocardial oxygen consumption. Changes in flow produce negligible changes in myocardial oxygen requirements unless total bypass of the venous return is approached.[5]

Since myocardial work is best related to myocardial oxygen consumption, the most effective system of reducing work would reduce systolic pressure. Any system for assisting the failing heart must also provide for adequate or increased coronary flow, since this determines the availability of oxygen to the heart. Although coronary flow occurs during both systole and diastole, more than two thirds of the total coronary flow occurs during diastole.[6,7] Thus, diastolic perfusion pressure and time must be maintained or, preferably, increased to aid the failing myocardium. The ideal system for assisting the heart would combine (1) a reduction of mean aortic systolic pressure, (2) a reduction of systolic time, (3) an increase in diastolic coronary perfusion pressure, and (4) an increase in diastolic perfusion time.

Venoarterial bypass to support the failing myocardium with or without an oxygenator in the system has been tried extensively in the laboratory and in a limited way clinically.[8,9] The principal effects of this method are the relief of flow work and the maintenance of an adequate mean aortic root pressure for coronary perfusion.[10,11] This has obvious

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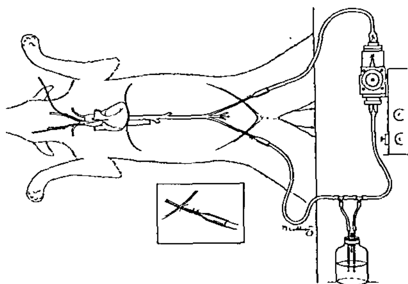


Fig. 3 Arterio-arterial technique for counterpulsation, using both femoral arteries This unidirectional flow produces less inertia.

artery, passes it through a ventricle with uniflow valves, and delivers it to the opposite femoral artery. The second circuit (Fig. 4) involves cannulation of a femoral artery or the abdominal aorta, with an extracorporeal circle circuit. The latter system seems preferable. This report deals with such a modified technique of arterial counterpulsation in circulatory and myocardial assistance. Studies of this circuit in use at heart rates from 80 to 190 per minute are reported. These results make us feel that counterpulsation assistance may be effective at any heart rate or rhythm.

Method and material

Mongrel dogs were anesthetized with intravenous pentobarbital and ventilated by a mechanical respirator through a cuffed endotracheal tube. Both carotid arteries were exposed, one for insertion of a polyethylene cannula into the aortic arch, the other for a stainless steel cannula passed through the aortic valve into the left ventricle. Aortic and ventricular pressures were monitored using Statham* strain-gauge pressure transducers, with a simultaneous electrocardiogram on a multichannel recorder. Femoral arteries or the abdominal aorta were exposed for insertion of the appropriate cannulas, depending on the system used. Prior to cannulation, heparin, 3 mg per kilogram, was administered intravenously.

The pumping equipment* used was identical with that described previously.[1] This can be set to act synchronously with the R wave of the electrocardiogram or to pump asynchronously at any desired rate and stroke volume (from 1 to 60 c.c.). When the pump is acting synchronously, the stroke ejection and aspiration may be timed for any portion of the pressure cycle by a delay mechanism. The duration of the stroke can also be controlled.

The ventricle used for both systems to be described is open at both ends, each of which contains a uniflow flutter valve. This was connected to the intra-arterial cannula or cannulas by Mayon† tubing which had a 3/32-inch wall thickness. Tubing with a one-half inch internal diameter was used for the afferent line of the ventricle, in order to keep filling impedance at a minimum. Tubing with a three-eights inch internal diameter can be used for the efferent line. In more recent experiments, thick-walled, nondistensible Tygon‡ tubing improved pressure transmission. To resolve the inertia problem as-

*Statham Instruments Co., Inc., Los Angeles, Calif.

*Davol Rubber Co., Providence, R. I.
†Mayon Plastics, Hopkins, Minn.
‡The U. S. Stoneware Co., Akron, Ohio

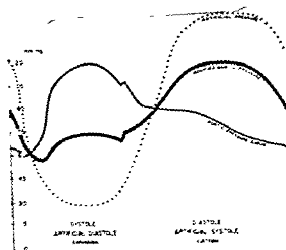


Fig. 1. Modification of the aortic pressure curve by the arterial counterpulsator. (From Clauss, et al., Journal of Thoracic and Cardiovascular Surgery, 41:447-458, 1961.)

advantages for the patient in circulatory shock but does very little to relieve the pressure work of the heart, which is working against the pressure produced by the arterial pump.[2]

Synchronized arterial counterpulsation is a method for reducing the pressure work of the heart. The theoretical design of synchronized arterial counterpulsation is illustrated by comparing the normal aortic pressure tracing to that expected from counterpulsation, namely, reversal of the systolic and diastolic pressure relationship (Fig. 1). In essence, systolic pressure is reduced by aspirating a portion of the stroke volume during the systolic ejection period of the heart and returning this same stroke volume during diastole, when the aortic valves are closed, to elevate or maintain the same diastolic pressure and thereby supply an adequate tissue and coronary perfusion while reducing the pressure work of the myocardium. The aortic valve must be competent in order to protect the left ventricle. Changes in left ventricular pressure should correspond to the changes in aortic systolic pressure.

Our initial experimental approach is illustrated diagrammatically in Fig. 2 and has been described in a previous communication.[3] This consists of a blind-ended ventricle connected to the arterial compartment by a cannula in the femoral artery in the human subject, or in the abdominal aorta in the dog. This requires only a simple surgical procedure, with minimal exposure of blood to an extracorporeal system. Appropriate hemodynamic responses were obtained, but further experience demonstrated limitations imposed by the heart rate. This reduced efficiency was apparently due to inertia to the rapid change in the direction of flow of the extracorporeal fluid volume. This volume was large in relation to the stroke change, and the elasticity of the system impeded effective alterations of systolic and diastolic pressures at higher heart rates. To correct this difficulty in a promising method of myocardial assistance, we have employed two alternative approaches. The first circuit (Fig. 3) takes blood from one femoral

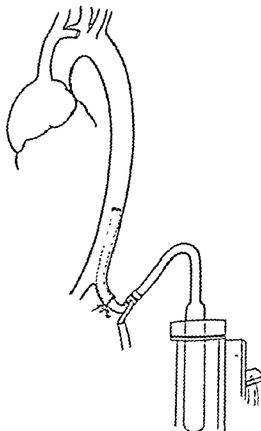


Fig. 2. A diagrammatic representation of a simple technique for counterpulsation. The femoral artery is cannulated under local anesthesia. The extracorporeal ventricle is synchronized to aspirate during systole and return the same blood volume during diastole. (From Clauss, et al., Journal of Thoracic and Cardiovascular Surgery, 41:447-458, 1961.)

systole as determined by opening and closure of the aortic valve leaflets. It remains unchanged. Electrical systole and diastole are also indicated for comparison. The prolongation of the control systole may be due to the fact that the dog was hypothermic at 32°C. The data in this tracing are detailed in Table I (heart rate, 80) and show significant changes in all important parameters. Systolic ejection time as determined in the aortic pressure tracing was reduced approximately 50 per cent. Peak aortic systolic pressure and left ventricular pressure were reduced 30 mm. Hg, and mean diastolic pressure was raised 10 mm. Hg, or about 16 per cent. Mean systolic pressure was reduced 27 mm. Hg, or 36 per cent of the control.

Systolic time varies with heart rate as well as with the changes produced by the pump; hence, similar experiments were carried out at rates which varied from 120 to 190 per minute.

The simultaneous changes in left ventricular pressures and aortic pulse tracings using counterpulsation at a heart rate of 120 per minute are shown in Fig. 6. Again, systolic time and pressure are indicated by the shaded areas. Note the marked change that occurred in left ventricular peak pressure and also in the aortic pulse pressure when counterpulsation was started. The

*Table I. Detailed description of the changes illustrated in the tracings of Fig. 5 (heart rate, 80), Fig. 6 (heart rate, 120), and Fig. 8 (heart rate, 180)**

	Heart rate of 80		*Heart rate of 120*		*Heart rate of 180*	
	Control	*C-P†*	*Control*	*C-P*	*Control*	*C-P*
Systolic ejection time (sec.)	0.32	0.14-0.19	0.19	0.14	0.11	0.11
Mean aortic systolic pressure (mm. Hg)	75	48	170	112	135	108
Mean aortic diastolic pressure (mm. Hg)	60	70	142	128	125	130
Peak aortic systolic pressure (mm. Hg)	80	50	175	155	142	115
Peak left ventricular pressure (mm. Hg)	80	50	180	125	173	148
Peak aortic diastolic pressure (mm. Hg)	65	105	160	165	130	147
Time-tension index	1,920	1,229	3,876	2,554	2,670	2,138

*These refer to single observations during separate experiments.
†Counterpulsation.

*Table II. The effect of counterpulsation on aortic pressure tracing**

Rate	*Control*				*Counterpulsation*			
	Systolic		*Diastolic*		*Systolic*		*Diastolic*	
	Pressure (mm. Hg)	*Time (sec.)*	*Pressure (mm. Hg)*	*Time (sec.)*	*Pressure (mm. Hg)*	*Time (sec.)*	*Pressure (mm. Hg)*	*Time (sec.)*
80 Hypothermia	75	0.32	60	0.42	48	0.14-0.19	70	0.58
120	170	0.19	142	0.30	112	0.14-0.16	128	0.36
120	145	0.19	125	0.34	113	0.15	123	0.36
130	168	0.17	142	0.30	143	0.14	168	0.33
170	140	0.10	125	0.21	118.9	0.11-0.12	138.3	0.20
180	135	0.11	125	0.22	108	0.11	130	0.23
190	103	0.11	90	0.21	93.1	0.12	101.4	0.20

*This is a list of single representative experiments at different heart rates to illustrate the changes in systolic and diastolic pressures and time.

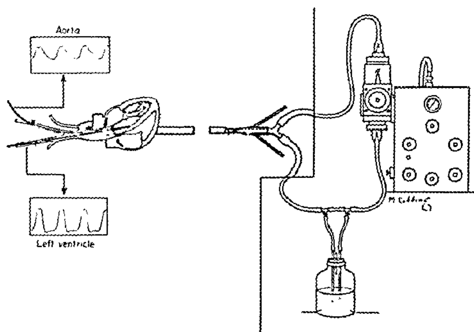


Fig. 4. Single cannula technique, using an extracorporeal circuit with uniflow valves in the ends of the ventricle. This has the advantage of a single cannula and reversal of flow limited to the single cannula.

sociated with rapid changes in direction of flow, arterio-arterial bypass utilizing the two femoral arteries was attempted (Fig. 3). The blood flow in this system is unidirectional. Blood is aspirated from one femoral artery during the animal's cardiac contraction and returned via the opposite femoral artery during diastole. The No. 12 to No 16F femoral cannulas offered excessive impedance to flow and therefore limited the volume of exchange and the desired alterations in pulse pressure. However, this circuit may be effective in human subjects when the vessels are larger.

The circuit used to obtain the changes in pulse pressure reported here consisted of a single aortic cannula with as large an internal diameter and as short a length as possible, connected to the pump circuit by a "Y" connector (Fig. 4). This is preferred in canine experiments. The system was primed with Ringer's solution or blood from the bottle reservoir, which was then excluded from the circuit. This system had the advantages of single cannulation and the reduction of inertia at high exchange rates, since flow is unidirectional except for the short central cannula. An especially constructed No. 24F or No. 26F flexible, thin-walled, noncollapsible plastic cannula was used.* The internal diameters (No. 24F or No. 26F) used were chosen because these have been used in large human femoral arteries. The abdominal aorta was used because the femoral arteries of dogs are small. This system has been used to study the effect of counterpulsation on systolic and diastolic pressures, and systolic time at heart rates which varied from 80 to 190 per minute.

Results

The results of synchronized counterpulsation at a heart rate of 80 are shown in Fig. 5. Systolic duration and pressure are indicated by the shaded areas. The duration of systole is timed from the opening of the aortic valve, as indicated by the aortic pulse tracing, to the closure of this valve, which is indicated by the dicrotic notch or rise in diastolic pressure produced by the pump. That the beginning of this second wave during counterpulsation represents the closure of the aortic valve is confirmed by comparison with simultaneous left ventricular pressures. It is important to note that intraventricular tension time does not correspond to the duration of

*Davol Rubber Co., Providence, R. I.

sociated with similar changes in aortic pressure and marked contraction of the pulse pressure. Counterpulsation reduced the aortic and ventricular pressures 17 per cent. The mean diastolic pressures remained at the same level.

Changes with counterpulsation at a rate of 180 per minute are presented in Fig. 8. The shaded areas indicate systolic time and pressure. Here the systolic time was actually increased slightly in several curves, mean systolic pressure was reduced 27 mm. Hg, and mean diastolic pressure was increased 5 mm. Hg during counterpulsation (Table I: heart rate, 180).

The effect of improper synchronization is illustrated in Fig. 9. The pump and heart systolic phases coincided on each alternate heartbeat of the dog. When they occurred simultaneously, the elevation in ventricular pressure corresponded to the rise in aortic pressure, since they were unicameral.

Mean systolic and diastolic pressures and systolic ejection times at varying rates and levels of pressure are presented in detail in Table II.

The changes produced in systolic pressure, diastolic pressure, and time-tension indices by counterpulsation are summar-

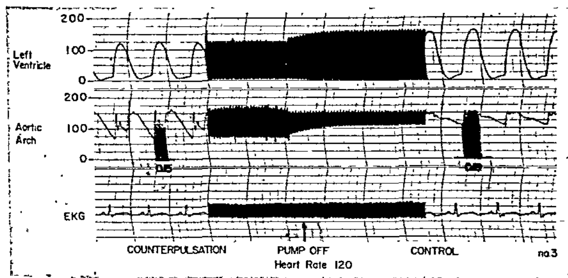


Fig. 7. Counterpulsation at a heart rate of 120 per minute. The magnitude of change in systolic and left ventricular pressures is less than that shown in Fig. 6 and is probably due to the difference in pressure.

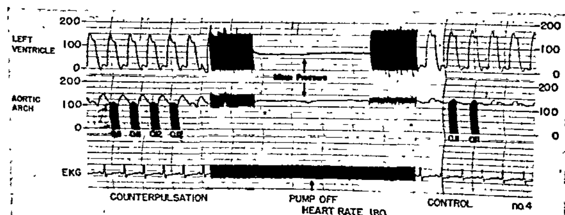


Fig. 8. Illustration of the significant reduction in systolic pressure despite the shortened systolic and d… periods at this rate. Mean arterial pressure remains unchanged.

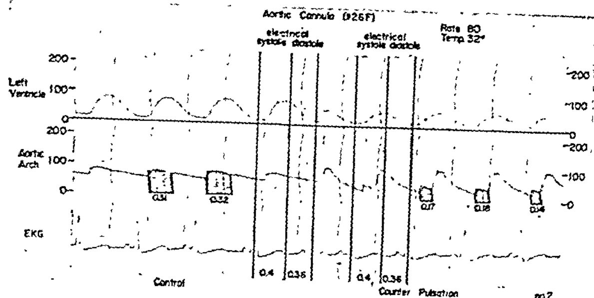


Fig. 5 Simultaneous recording of pressures in the aortic arch and left ventricle, with the electrocardiogram used to guide counterpulsation. The shaded areas represent the systolic ejection period and demonstrate the marked changes in pressure and duration when the synchronized pump is turned on.

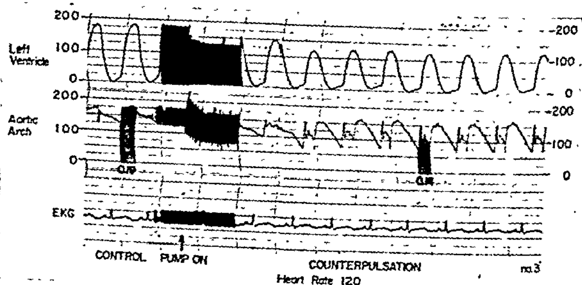


Fig. 6 Synchronized counterpulsation at a rate of 120 per minute. The slow tracing at the time counterpulsation was started illustrates the marked reduction in left ventricular pressure and widened pulse pressure. Shaded areas indicate systolic pressure and time.

results of this experiment are shown in Table I (heart rate, 120). The duration of the systolic ejection period was shortened moderately (0.05 second) on counterpulsation, but the mean aortic systolic pressure was reduced 58 mm. Hg from a control of 170 mm. Hg. This is a reduction of 34 per cent in mean systolic pressure. Mean diastolic pressure was reduced 14 mm. Hg despite counterpulsation, because of the marked reduction in systolic pressure. The changes in the same animal at a different level of pressure when counterpulsation was discontinued are shown in Fig. 7. It is impressive that the ventricular peak pressure of 125 mm. Hg on counterpulsation rose to 160 mm. Hg when counterpulsation was discontinued. This was as-

systolic pressure is lowered and diastolic pressure is normal or elevated. The specific alterations of systolic pressure, diastolic pressure, and diastolic time produced by synchronized arterial counterpulsation meet requirements which are considered to be favorable to cardiac assistance. This has been accomplished at pulse rates from 80 to 190. The two experimental circuits described here represent simple practical techniques involved in the reduction of pressure work.

The use of a single intra-arterial cannula connected to a ventricle by a "Y" connector is effective under laboratory conditions. Experience in human beings indicates that it is important to have the tip of the femoral cannula in the aorta, both as a reservoir of blood and as a conduit for changes in pressure to the heart. Experimentally, the magnitude of change increases as the tip of the cannula approximates the aortic valve. The direction of flow in this system is unidirectional except for that in the cannula, wherein rapid changes in direction of flow must occur synchronously with the heartbeat. The fluid medium in the extracorporeal system, be it lactated Ringer's solution or blood, acts principally as a transmitter of changes in pressure. There is very little flow of blood through the system, and this reduces trauma to blood.

The range of changes in blood pressure and heart rate reported here is representative of what may be encountered clinically. Reduction of systolic pressure and elevation or maintenance of diastolic pressure have been easily and consistently produced. The extent of changes assumed to be favorable to myocardial pressure work and oxygen consumption assistance vary with the heart rate, the systolic time, and the volume of blood that can be aspirated from the arterial tree (which, in turn, depends on the size of the cannulas). Although the largest per cent reduction in control systolic pressure occurred at a rate of 80 (37 per cent), it is significant that it was reduced 34.1 per cent at a rate of 120, and 20 per cent at a rate of 180. These should be significant clinically. The reduction in systolic pressure and elevation of diastolic pressure indicate that marked reduction in pressure work can be achieved in an animal with simultaneous increase in or maintenance of adequate coronary and systemic perfusion.

Changes in systolic ejection time do not correspond to changes in the intraventricular tension time, a fundamental index of myocardial oxygen consumption. The counterpulsator can prematurely close the aortic valve by raising aortic pressure above that being developed by the ventricle. The ventricle continues to contract and produce pressure, although at a lower level. The tension-time index is a generally useful and reliable index of myocardial oxygen consumption, but here one must deal with mechanical alterations of systolic ejection time that may make it invalid for use in calculating time-tension index. For this reason the systolic time measured on the control tracing was used in calculating the time-tension indices. Although systolic ejection time may be reduced as much as 50 per cent by premature closure of the aortic valve during counterpulsation, it does not affect the desired reduction in left ventricular pressure. This presumably is due to more rapid emptying of the ventricle during the first half of systole by pump aspiration. The magnitude of change in mean systolic pressure is the best indicator of the degree of myocardial assistance that has been effected.

Summary

Two simplified techniques of cannulation for arterial counterpulsation have been described. The preferred technique involves a short femoral or direct aortic cannula connected to a "Y" tube, the limbs of which are connected to a ventricle with uniflow valves. This circuit reduces the damping of fluid inertia in counterpulsation. With this technique, several conclusions can be drawn as to the efficacy of assisted circulation.

1. Synchronized arterial counterpulsation can reduce mean aortic systolic pressure and maintain or elevate the mean diastolic pressure. This meets some of the physiologic criteria for myocardial assistance.

2. Experimental application of this technique at heart rates varying from 80 to 190 per minute demonstrated effective reduction of mean systolic pressure, shortening

Table III. The magnitude of change in aortic systolic and diastolic mean pressures, and the corresponding changes in time-tension indices

Rate	Systolic level (mm Hg)	Systolic reduction		Change in diastole (mm. Hg)	Time-tension index	
		mm Hg	%		Control	Counterpulsation
80	75	27	36	+10	1,920	1,229
120	170	58	34.1	−14	3,876	2,554
120	145	32	22	−2	3,306	2,576
130	168	25	15.4	+25	3,713	3,160
170	140	21	15	+13	2,380	2,023
180	135	27	20	+5	2,670	2,138
190	103	10	9.7	+14	2,348	2,123

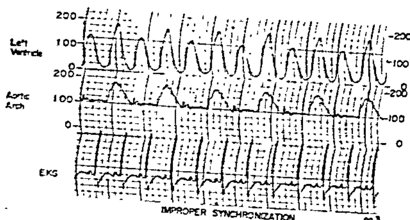


Fig. 9. The tall ventricular and aortic peaks represent the result of simultaneous ventricular and pump contractions on alternate beats. The unaltered aortic tracing is seen in the troughs between the pump ejections.

ized in Table III. Significant reduction in mean systolic pressure was obtained at all levels of aortic pressure and heart rates. This varied from 36 per cent of the control at a heart rate of 80 to 9.7 per cent of the control at a heart rate of 190. The magnitude of reduction in systolic pressure decreased as the rate increased. The reduction of 58 mm. Hg would indicate that the level of control blood pressure was also a factor in the magnitude of absolute change obtained.

Diastolic pressure was actually elevated in 5 out of 7 experiments. There was significant reduction in only one, and this was associated with the largest reduction in systolic pressure that was obtained, namely, 58 mm. Hg. The changes in systolic ejection time were significant only at the slow rate of 80 under conditions of hypothermia. The ejection time and premature closure of the aortic valves progressively shortened as the rate was increased to 180 beats per minute. Beyond this point there was no change.

Discussion

Ideal cardiac assistance requires reduction of pressure work and myocardial oxygen need while coronary perfusion is maintained or increased. Simple reduction of pressure is not enough, because lowered mean aortic pressure or diastolic pressure results in decreased coronary flow, and this might alter unfavorably the balance of myocardial oxygen demand and supply. Synchronized counterpulsation should reverse the pulse pressure curve so that

Assisted circulation. III. The effect of synchronized arterial counterpulsation on myocardial oxygen consumption and coronary flow

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Synchronized arterial counterpulsation can reduce aortic systolic pressure and elevate diastolic pressure. This ability to reverse the aortic pressure curve enables us to reduce left ventricular work and mean aortic pressure while maintaining systemic and coronary flow by elevation of diastolic pressure against a closed aortic valve.

This report is concerned with extension of previous studies to the direct measurement of myocardial oxygen consumption using coronary sinus flow in open-chest dogs with an intact beating heart. This preparation also proved valuable in differentiating the role of systolic pressure, diastolic pressure, and mean aortic pressure versus myocardial oxygen consumption as determinants of coronary flow.

Materials and methods

The preparation is identical to that described in the previous article (*Assisted Circulation. II*), except for the technique of measuring coronary sinus flow (Fig. 1). The heart was exposed through a thoracotomy in the right sixth intercostal space. The coronary sinus was cannulated through the right atrial appendage with a No. 16F plastic catheter. The coronary sinus ostium was occluded about the catheter by an external circumferential suture. Coronary sinus flow was allowed to drain by gravity into a previously primed reservoir and returned to the animal through a cannula in a femoral vein by means of a rotary pump. Measurements of coronary flow were made inter-

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of systolic ejection time, and elevation of diastolic pressure.

3. The degrees of change vary with the heart rate and, to some extent, with the control pressure. The per cent reduction in control systolic pressure by counterpulsation varied from 36 per cent at a rate of 80 beats per minute to 9.7 per cent at a rate of 190 beats per minute.

4. Reduction in systolic ejection time is produced mechanically when the pump raises the blood pressure during diastole. This probably does not necessarily represent actual shortening of systolic contraction time.

5. Changes in diastolic pressure vary with the magnitude of changes in the mean aortic systolic pressure. The pressure and duration of diastole are usually higher than the control and indicate increased coronary perfusion associated with reduced pressure work.

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Table I. The hemodynamic and metabolic data from 17 paired experiments in 8 dogs

Experiment		Coronary A-V difference (vol. %)	Coronary sinus flow (c.c./min.)	Myocardial oxygen consumption (c.c./min.)	Mean systolic pressure (aorta)	Mean diastolic pressure (aorta)	Mean arterial pressure	Left ventricular peak pressure	Systolic time (sec.)	Heart rate (min.)	Body temperature (°C)
1. I											
	C	7.05	36	2.54	87	77	80	90	0.20	100	30
	CP	4.52	36	1.63	50	80	70	55	0.095	100	30
2. II											
	C	8.20	35	2.87	95	82	88	107	0.33	90	30
	CP	4.43	42	1.86	45	80	45	70	0.25	90	30
3. II											
	C	4.34	38	1.65	85	77	85	105	0.27	100	30
	CP	4.69	28	1.31	35	65	50	50	0.22	100	30
4. II											
	C	7.33	28	2.05	90	80	85	103	0.33	90	30
	CP	4.58	28	1.28	35	60	55	58	0.19	90	30
5. III											
	C	7.02	46	3.23	105	92	97	97	0.30	100	30
	CP	6.24	44	2.75	45	75	65	50	0.20	100	30
6. III											
	C	9.47	36	3.41	82	70	72	75	0.30	100	30
	CP	7.04	38	2.68	40	62	60	40	0.20	100	30
7. IV											
	C	9.80	20	1.96	92	60	67	75	0.24	70	24
	CP	4.20	30	1.26	40	75	55	45	0.24	70	24
8. IV											
	C	10.62	26	2.76	97	80	77	92	0.24	70	24
	CP	3.92	34	1.33	32	75	60	40	0.24	70	24
9. V											
	C	10.84	48	5.20	115	98	105	120	0.24	95	30
	CP	8.66	54	4.68	80	95	95	80	0.18	95	30
10. V											
	C	10.71	52	5.57	130	110	120	130	0.24	95	29
	CP	8.52	52	4.43	82	100	95	90	0.16	95	29
11. V											
	C	10.62	44	4.67	82	72	80	80	0.24	95	28.5
	CP	10.32	44	4.54	55	80	75	60	0.18	95	28.5
12. VI											
	C	11.36	46	5.23	125	115	110	—	0.25	100	—
	CP	7.66	54	4.14	85	105	95	—	0.13	100	—
13. VI											
	C	12.92	33	4.26	97	92	92	—	0.25	100	—
	CP	9.35	42	3.93	70	90	90	—	0.17	100	—
14. VI											
	C	13.49	30	4.05	97	92	92	—	0.25	100	—
	CP	11.73	32	3.75	55	75	75	—	0.19	100	—
15. VII											
	C	10.89	36	3.92	80	72	75	—	0.16	105	—
	CP	9.49	35	3.32	57	70	70	—	0.16	105	—
16. VII											
	C	11.52	44	5.17	78	72	75	—	0.21	120	—
	CP	10.07	36	3.62	70	85	75	—	0.09	110	—
17. VIII											
	C	11.35	22	2.50	143	133	140	—	0.17	170	—
	CP	10.80	19	2.03	90	127	115	—	0.06	170	—

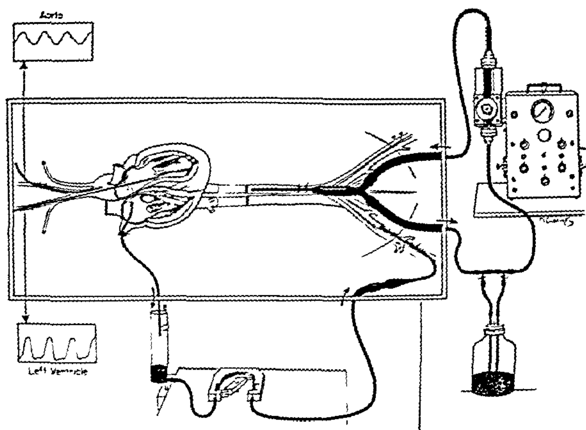


Fig. 1. This is a modification of our previous experimental design to include coronary sinus bypass through an extracorporeal system.

mittently by directing the gravity drainage coronary venous blood into a graduate. Pressures were measured using Statham* pressure transducers and were recorded simultaneously with the electrocardiogram on a multichannel direct-writing recorder. Coronary arteriovenous oxygen difference was determined by obtaining simultaneous samples of blood from the aortic arch and from the coronary-sinus return collected in oiled, heparin-containing syringes. Oxygen saturation and oxygen capacity were determined using a Beckman† spectrophotometer. Oxygen content was calculated. All controls were recorded immediately before or immediately after the counterpulsation. Hypothermia was induced by surface cooling in 3 dogs to slow the heart rate. Body temperatures were measured using an esophageal thermocouple.

*Statham Instrument Co., Inc., Los Angeles, Calif.
†Beckman Instruments, Inc., Fullerton, Calif.

Results

Counterpulsation was performed at heart rates which varied from 70 to 170 per minute. Body temperatures varied from 24 to 30 degrees centigrade. The latter temperature was the result of an open chest exposed to room temperature and the cooling effect of the extracorporeal venous circuit.

The data in Table I are derived from 17 pairs of determinations (control and counterpulsation) in 8 experiments. Mean systolic pressure was reduced by counterpulsation from 8 to 65 mm. Hg. These represented a reduction of control systolic mean pressures from 10 to 67 per cent, with an average reduction of 41 per cent. The reduction in pressure was not related to the heart rate. Changes in left ventricular pressure corresponded to the change in systolic pressure illustrated in Fig. 2 by the shaded areas beneath the aortic pressure curve.

Reduction in myocardial oxygen con-

was associated with a 36 per cent reduction in myocardial oxygen consumption at a heart rate of 70, whereas in Experiment 3, a 59 per cent reduction in systolic pressure was accompanied by only a 21 per cent reduction in myocardial oxygen consumption at a heart rate of 95. This variation is independent of the heart rate.

The response of coronary sinus flow to counterpulsation showed rather wide variation. It was increased in 8 (47 per cent), unchanged in 4 (24 per cent), and decreased in 5 (29 per cent). The average change for the group of experiments was +1.8 c.c. per minute and not significant. The corresponding changes in mean diastolic pressure, peak diastolic pressure, and coronary sinus flow are shown in Table II.

Peak diastolic pressures were elevated on counterpulsation in all experiments and ranged from +3 to +60 mm. Hg above the controls (average +26 mm. Hg). On the other hand, mean diastolic pressures were decreased in 13 experiments and elevated in 4, with a variation from −17 to +15 mm. Hg, and with an average change of −3.6 mm. Hg. This minor change in mean diastolic pressure corresponds well with the insignificant change noted in mean coronary sinus flow.

Mean arterial pressures were uniformly reduced on counterpulsation, with one exception. This reduction varied up to 43 mm. Hg, without corresponding reduction in coronary flow. The greatest reduction in mean arterial pressure was associated with increased coronary flow (Table I, Experiment 2). Coronary A-V oxygen difference was markedly and consistently decreased by counterpulsation. Although this varied with the degree of change produced in coronary flow, the reduction varied up to 5.60 ml. of oxygen per 100 ml. of blood. In general, the reduction of A-V oxygen difference corresponded in magnitude to the reduction in systolic pressure. Table III summarizes the physiologic effects of counterpulsation at normotensive and mild hypothermic levels.

Discussion

The value of synchronized counterpulsation depends on its ability to reduce myocardial work, specifically by the reduction of pressure work while maintaining or increasing coronary and systemic flow. The use of oxygen metabolism as an index of the production of energy by the heart probably represents the best direct method of evaluating the effectiveness of any procedure to assist the heart.[1,2] The experimental preparation described here, using an intact beating heart, was selected to insure the least disturbance of normal reflex and metabolic pathways while inducing the desired alterations in pressure.

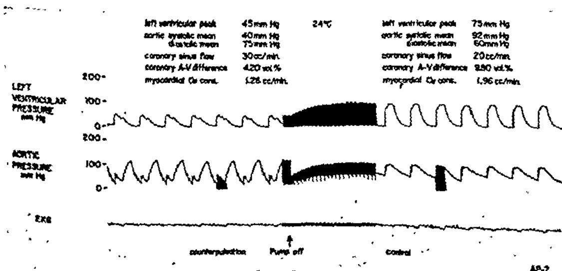


Fig. 4. Aortic systolic mean pressure is reduced 48 per cent, and myocardial oxygen consumption is reduced 36 per cent by counterpulsation.

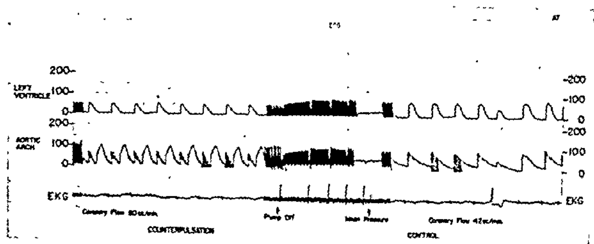


Fig. 2. Coronary sinus flow is nearly double the control during counterpulsation because of the remarkable elevation in diastolic pressure to 100 mm. Hg from a control of 55 mm. Hg. The heart rate is 60 per minute.

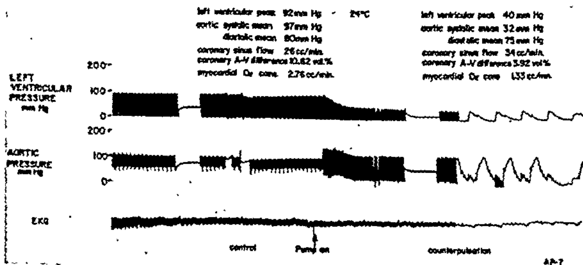


Fig. 3. Aortic systolic mean pressure is reduced 67 per cent by counterpulsation, and myocardial oxygen consumption is reduced 52 per cent. This was accomplished with an actual increase in coronary sinus flow. Note the marked reduction in coronary A-V oxygen difference and left ventricular pressure during counterpulsation.

sumption as calculated from the coronary A-V oxygen difference and coronary sinus flow was more variable. Myocardial oxygen consumption was reduced from 0.13 to 1.55 ml. of oxygen per minute. This represented from 3 to 52 per cent of the control, with an average reduction of 23.2 per cent. Changes in myocardial oxygen consumption, systolic pressure, diastolic pressure, left ventricular pressure, coronary sinus flow, and coronary A-V oxygen differences are illustrated in Figs. 3 and 4. These show dramatic changes in all these parameters with counterpulsation. Fig. 3 represents the most marked changes, with a 67 per cent reduction in systolic pressure and a 52 per cent reduction in myocardial oxygen consumption. This was associated with an actual increase in coronary sinus flow and a marked decrease in coronary A-V oxygen difference. The correlation of myocardial oxygen consumption to the reduction of systolic pressure is shown in Fig. 5. The magnitude of change in myocardial oxygen consumption does not consistently reflect the change in systolic and left ventricular pressures. Thus, in Experiment 1, a 43 per cent reduction in mean systolic pressure

changed or was actually increased in 12 of the 17 experiments despite a reduction in mean arterial pressure. This was directly related to the changes accomplished in diastolic pressure and time. It did at times produce a marked increase in coronary flow, such as in Fig. 2, where it was approximately doubled.

The mechanical shortening of systolic time and lengthening of diastolic time was a consistent finding. This did not interfere with the desired reduction in left ventricular pressure because of the more rapid emptying due to extracorporeal assistance and provided additional diastolic time for coronary flow. This may account for the favorable balance of coronary flow in spite of a reduction in mean arterial pressure.

The reduction in mean arterial pressure with counterpulsation depended on the magnitude of change accomplished in systolic pressure despite the compensatory increase in diastolic pressures. Although the change varied considerably (0 to 43 mm. Hg), the average reduction was but 17.6 mm. Hg. This again reflects the reduced pressure work of synchronized counterpulsation, without corresponding decreases in coronary flow.

The salutary effect of the reduction in pressure work, the reduction in myocardial oxygen utilization, and the maintenance of coronary circulation by counterpulsation marks it as an ideal physiologic tool to assist the heart, whether failure be due to myocardial infarction, arteriosclerotic heart disease, or hypertension. Experimentally, its effectiveness has been demonstrated by Jacobey and associates[8] when applied to induced myocardial infarction in dogs, with reduction of mortality from 80 to 20 per cent. Clinical studies are in progress.

Summary

1. Synchronized arterial counterpulsation is an effective method for reducing mean systolic pressure and myocardial oxygen consumption while maintaining coronary perfusion.

2. Further evidence is presented to emphasize the dominant role of pressure work as the determinant of myocardial oxygen consumption in the intact beating heart.

3. Coronary flow can be altered by changes in diastolic pressure, irrespective of myocardial oxygen need or metabolism.

4. Arterial counterpulsation appears to be an excellent method of assisting the failing myocardium and merits further investigation and application.

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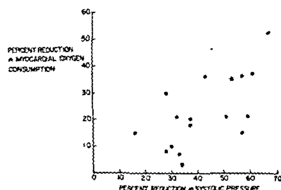


Fig. 5. Correlation between the per cent reduction in mean systolic pressure and the per cent reduction in myocardial oxygen consumption accomplished by counterpulsation.

Coronary sinus outflow represents the major venous drainage of the heart and has been found to correctly reflect significant changes in total coronary inflow with the intact beating heart.[3] Although the coronary sinus outflow represents a variable proportion of the total inflow in each dog, this was not thought to be a source of inaccuracy, since control determinations were performed on the same heart.

Counterpulsation synchronized with the electrocardiogram is an ideal method of selectively reducing systolic pressure by extracorporeal aspiration and elevating diastolic pressure by returning this same volume during the diastolic phase. Coronary and systemic flow are thus maintained independent of left ventricular work in an intact beating heart. Our data clearly corroborate the relationship of systolic pressure work to myocardial oxygen consumption. In general, a reduction in systolic pressure is associated with a similar reduction in myocardial oxygen consumption, which is best shown by the marked reduction in coronary A-V oxygen differences with counterpulsation. The fact that there is some variation in the correlation of pressure and oxygen consumption indicates other variables, such as flow work, the position of the arterial cannula, and the location of aspiration and return in the cardiac pressure cycle.

Studies of phasic coronary flow have demonstrated its predominance during diastole, when the extravascular pressure is reduced.[4] Although myocardial oxygen need or utilization has been emphasized as the prime determinant of coronary flow, rather than the mechanical action of pressure,[5,6] the pressure at the coronary ostia is known to alter coronary flow, independent of myocardial oxygen consumption.[7] Synchronized arterial counterpulsation alters systolic pressure, diastolic pressure, the duration of systole and diastole, and coronary flow, independent of myocardial oxygen consumption. The marked reduction in systolic pressure and myocardial oxygen consumption during counterpulsation was, in general, associated with changes in coronary flow in the opposite direction. Coronary flow remained un-

Table II. The effect of changes in peak and mean diastolic pressures of the aorta on coronary sinus flow during counterpulsation

	Changes in peak diastolic pressure (mm Hg)	Changes in mean diastolic pressure (mm. Hg)	Changes in coronary sinus flow (c.c./min)
1	+33	+3	0
2	+28	−2	+7
3.	+12	−8	−10
4.	+30	−10	0
5	+3	−17	−2
6	+20	−8	+2
7	+60	+15	+10
8	+40	−5	+8
9.	+37	−3	+6
10.	+30	−10	0
11.	+58	+8	0
12	+20	−10	+8
13.	+18	−2	+9
14.	+3	−17	+2
15.	+13	−2	−1
16.	+33	+13	−8
17.	+12	−6	−3
Average	+26	−3.6	+1.8

Table III. The physiological effects of counterpulsation at normotensive and mild hypothermic levels

Coronary flow	Unchanged
Mean systolic pressure	Decreased
Mean diastolic pressure	Unchanged
Peak diastolic pressure	Increased
Mean arterial pressure	Decreased
Coronary A-V difference	Decreased
Myocardial oxygen consumption	Decreased

preamplifier of a multichannel oscilloscopic recorder. With this system, cuff pressure was recorded simultaneously by means of a Statham P23AA pressure transducer. When arterial pressure was determined simultaneously from two or more limbs by the plethysmographic method, a common source of pressure was employed for the occluding cuffs.

To increase the adaptability of the plethysmograph to office and bedside situations (Fig. 2), an inexpensive direct-current Wheatstone bridge and transistorized amplifier, powered by mercury batteries, were designed* (Fig. 3). The plethysmograph is connected to this circuit, which, in turn, leads to the direct-current input terminal of a portable electrocardiographic recorder (Fig. 2). Cuff pressure is determined visually from the sphygmomanometer and may also be recorded by pressing the marker control of the ECG recorder, at intervals of 5 or 10 mm. Hg as the pressure falls. Systolic pressure can also be determined by noting the cuff pressure at which the balanced meter dial on the circuit box is deflected to the right.

The accuracy of the plethysmographic technique was determined in 15 patients who ranged in age from 17 months to 53 years, by simultaneously recording brachial arterial pressure through a Cournand needle in the opposite extremity In 6 of the patients (including 5 with coarctation of the aorta in whom the diagnosis was subsequently confirmed at operation) the plethysmograph was also applied to the calf, and the pressure obtained was compared to that simultaneously recorded in the femoral artery. In addition, measurements of systolic arterial pressure have been carried out by the plethysmographic technique in a variety of other patients; these included infants, patients in whom an aortic coarctation had been repaired, patients in postoperative shock, and patients with peripheral vascular disease

Blood flow in the forearm or calf was measured with the transistorized DC amplifying system and an electrocardiographic recorder by the venous occlusion technique.[4] The sphygmomanometer cuff was inflated to a value just below arterial diastolic pressure, and by this technique the flow of blood into the limb, expressed in milliliters per 100 grams per minute, was directly proportional to the initial slope of increase of the circumference of the limb, according to the method of Holling.[5] When desired, the flow of blood into the hand or foot could be eliminated by inflating to suprasystolic pressure a cuff placed around the wrist or ankle.

Results and discussion

In the 15 measurements of brachial arterial pressure, the systolic pressure determined by the plethysmographic technique differed from the intra-arterial pressure by −16 to +10 mm. Hg. (Fig. 4). The differences averaged −2.1 mm. Hg, and in 12 of the 15 patients the plethysmographic pressure was within 5 mm. Hg of the simultaneously recorded systolic intra-arterial pressure. In the 6 patients in whom femoral arterial pressure was measured, the pressure determined plethysmographically differed from the needle pressure by −5 to +16 mm. Hg, with an average difference of +2.1 mm. Hg.

An example of brachial arterial pressure recorded from the right arm by means of a Cournand needle, and from the left arm by means of the mercury strain-gauge plethysmograph, in a child with a functional heart murmur who was undergoing *transseptal left heart catheterization, is* illustrated in Fig. 5. The calibrations of the left ventricular pressure, the intra-arterial pressure, and of the pressure recorded from the occluding cuff were all set at identical sensitivities, and the same base line was employed. It is evident that the circumference of the forearm began to increase when the pressure within the occluding cuff fell to 108 mm. Hg, i.e., to the peak level of systolic pressure in the brachial artery and left ventricle.

A practical application of the plethysmographic technique is illustrated in Fig. 6, which was obtained from a 6-month-old infant at the time of cardiac catheterization. The catheter entered a ventricle in which the systolic pressure averaged 78 mm. Hg. Since it was important to de

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A simplified plethysmographic system for the measurement of systemic arterial pressure and peripheral blood flow

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The accurate measurement of systolic arterial pressure may be difficult or even impossible in a number of clinical settings. Thus, most physicians have not found the auscultatory technique to be uniformly satisfactory in patients with markedly depressed cardiac outputs, in patients in whom the systemic vascular bed is constricted, and in those in whom an organic obstruction exists in the arterial bed. In addition, this technique is notoriously unreliable for the measurement of arterial pressure in infants and young children

In 1953, Whitney[1] described a simple mercury strain-gauge phethysmograph designed to measure blood flow in the limbs. Holling and associates[2] recently modified the instrument and its method of calibration and presented a number of important applications of this device in the study of patients with peripheral vascular disease. The purpose of this paper is to: (1) describe the technique and accuracy of the measurement of systolic arterial pressure by the mercury strain-gauge plethysmograph, (2) illustrate the usefulness of the method in the preoperative and postoperative study of patients with coarctation of the aorta, and (3) describe a simple, inexpensive, and practical modification of the circuit which permits the use of the instrument in conjunction with commercially available electrocardiographic recorders.

Methods

A single-strand, mercury-filled rubber strain-gauge plethysmograph of the type described by Holling[2] was employed (Fig. 1). Systolic arterial pressure is determined by wrapping the mercury gauge around the forearm or calf, securing it with adhesive tape, inflating to suprasystolic pressure a standard sphygmomanometer cuff wrapped around the upper arm or thigh, and then slowly releasing the pressure from the cuff. When the cuff pressure falls to the systolic level, blood flows into the limb, and the circumference of the limb suddenly begins to increase. As a result the column of mercury within the rubber tubing elongates, producing an increase in resistance to current offered by the column, which, in turn, results in a sharp upward deflection of the recording galvanometer.

Two basic types of amplifying and recording systems were employed. In the first, an Elsner impedance matching circuit[3] and Wheatstone bridge were employed in conjunction with an AC carrier

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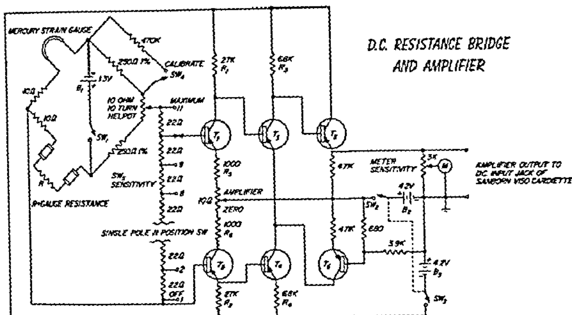


Fig. 3. Circuit diagram of transistorized DC amplifier.

termine whether this chamber was the right or the left ventricle, the simultaneous determination of systemic arterial pressure was considered to be necessary. A needle could not be inserted into a peripheral artery by percutaneous puncture, and instead of exposing an artery surgically, systolic arterial pressure was measured by the plethysmographic technique. It was clear that the systolic arterial pressure in the calf exceeded the ventricular systolic pressure, thus identifying the chamber as the nonsystemic (right) ventricle. Hence, the plethysmographic technique obviated a more complex and time-consuming maneuver (exposure of a systemic artery) in a seriously ill infant.

Pressures recorded simultaneously in the upper and lower extremities of a 22-month-old infant are reproduced in Fig. 7. After examination by conventional techniques, this patient had been referred to the National Heart Institute because systemic hypertension was suspected. The plethysmographic study not only excluded significant hypertension, but, since the pressure in the calf exceeded that recorded from the forearm, coarctation of the aorta could also be ruled out.

The potential value of the plethysmographic technique in the study of patients with coarctation of the aorta is illustrated in Figs. 8, 9, and 10. Direct arterial pressures from the brachial and femoral artery, together with plethysmographically recorded pressures from the opposite forearm and calf in a 14-year-old girl are reproduced in Fig. 8. Large differences in systolic pressures between the arm and leg were present both by the direct and by the indirect methods. Although it may frequently be difficult to insert a needle into the femoral artery of patients with coarctation of the

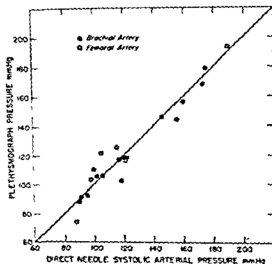


Fig. 4. Comparison of systolic pressures recorded directly through an intra-arterial needle and by means of the plethysmograph.

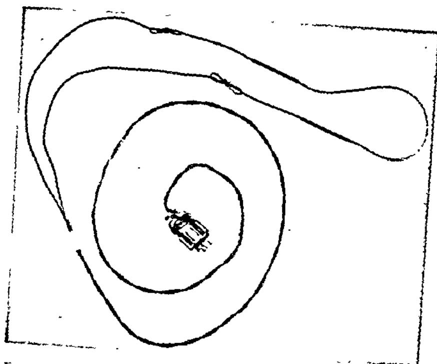


Fig. *1.* Photograph of mercury strain-gauge plethysmograph.

Fig. 2. Photograph showing plethysmograph (*1*) and occluding cuff (*2*) in place. *3*, Sphygmomanometer. *4*, Transistorized DC amplifier. *5*, ECG recorder.

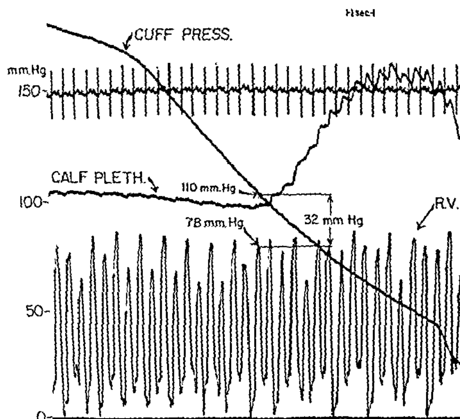


Fig. 6. Recordings obtained by catheterization of the right side of the heart in a 6-month-old infant. *R.V.*: Right ventricular pressure. *110 mm. Hg*, Represents the arterial pressure in the calf since it was at this cuff pressure that the plethysmographic tracing rose. *32 mm Hg*, Represents the difference between right ventricular and systemic arterial systolic pressures

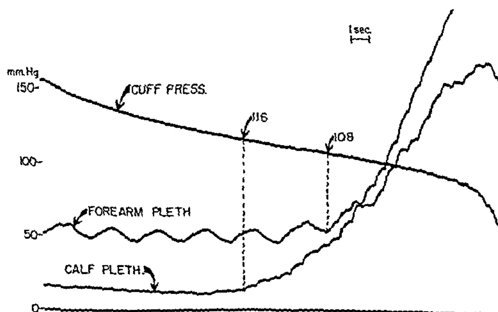


Fig. 7. Simultaneous recordings obtained from forearm and calf plethysmographs in the 22-month-old child described in the text

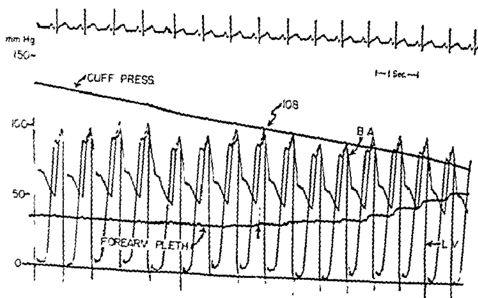


Fig. 5. Simultaneous left ventricular (*L V.*), brachial arterial (*B.A.*), cuff pressure (*cuff press.*), and forearm plethysmographic (*forearm pleth.*) tracings recorded in a 6-year-old boy.

aorta, the plethysmographic technique offers the opportunity to record precise systolic pressures in the lower extremities of these patients. Fig. 9 illustrates pressures recorded simultaneously from the upper and lower extremities by the plethysmographic technique in a 17-year-old boy. A gradient of 42 mm. Hg is evident, which confirms the clinical diagnosis of coarctation of the aorta. After operation, this gradient was markedly decreased (Fig. 10), which indicated that the operation had been successful in relieving the obstruction.

The plethysmographic tracings obtained with a portable electrocardiographic recorder, utilizing the transistorized DC amplifier are shown in Figs. 11 and 12. In Fig. 11, systolic arterial pressure in the forearm is indicated by the change in slope of the tracing, and is related to the pressure in the occluding cuff, indicated by the marker at intervals of 5 mm. Hg. Application of the DC amplifier and ECG recorder for the measurement of blood flow in the forearm is illustrated in Fig. 12. Flow rose from a level of 2.01 ml. per 100 Gm. per minute during the control period to 8.34 ml. per 100 Gm. per minute after a brief period of exercise of the forearm. After immersion of the hand into ice water for 1 minute, the blood flow in the forearm declined to 1.27 ml. per 100 Gm. per minute.

Comment

In this study the mercury strain-gauge plethysmograph was found to be an accurate and simple clinical device with which to measure systolic arterial pressure and blood flow in the forearm or calf. In order to identify the base line accurately, artifacts which result from muscular movements must be avoided. In infants it is helpful to wait for a short period after the cuff and plethysmograph have been applied, until the infant is quiet; sometimes, bottle feeding is helpful. Regular, slow rhythmic changes in the base line of the plethysmograph pulse wave, which are due to sympathetic vasomotor activity and are accentuated by respiration,[5] are seen occasionally in normal patients. These mild fluctuations do not interfere with the determination of arterial pressure or of blood flow.

The high sensitivity, alternating-current amplifying system is particularly useful for the monitoring of systemic pressure in infants who are undergoing cardiac catheterization or surgery. This system is applicable in situations in which it is difficult or undesirable to insert an intra-arterial needle directly, such as in the evaluation of coarctation of the aorta or of occlusive peripheral vascular disease. In addition, when two plethysmographs are employed, it permits the simultaneous

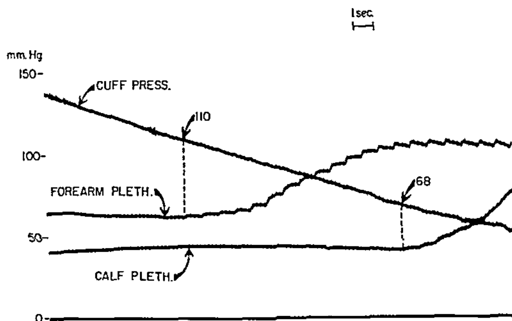


Fig. 9. Arterial pressures recorded from the forearm and calf by the plethysmographic technique in a 17-year-old boy with coarctation of the aorta.

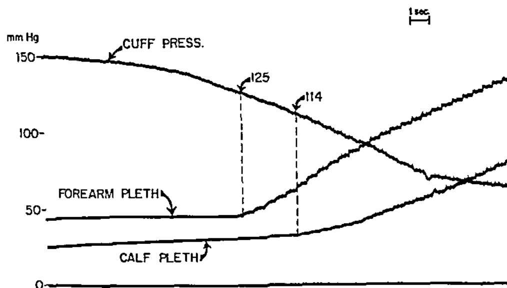


Fig. 10. Plethysmographic recordings obtained after resection of the coarctation in the patient whose preoperative tracings are reproduced in Fig 9

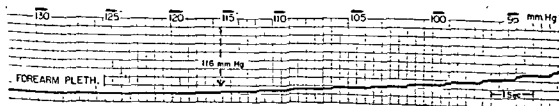


Fig. 11. Plethysmographic recording from the forearm of a 27-year-old man The transistorized DC and a commercial ECG recorder w

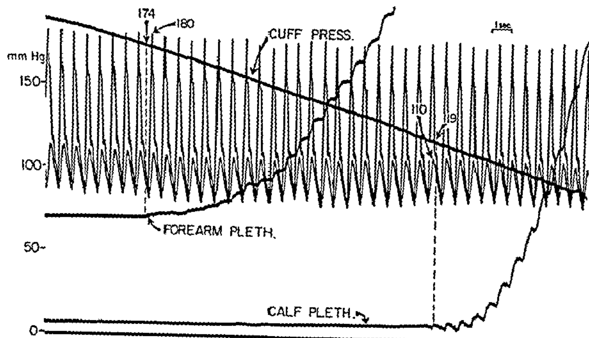


Fig. 8. Pressures recorded simultaneously from the brachial and femoral arteries through intra-arterial needles and from the forearm and calf by means of two plethysmographs in a 14-year-old girl with coarctation of the aorta.

recording of the systolic pressures in two limbs.

The development of the transistorized DC amplifier and Wheatstone bridge permits the recording of systolic arterial pressure and of blood flow in the limbs with a standard portable electrocardiographic recorder at the bedside or in the physician's office. The total cost of the parts required for construction of the circuit is approximately $40. Any of the commercially available recorders which are equipped with a DC input plug may be employed. The availability of an inexpensive and simple yet reliable system with which to measure blood flow in the limbs at the bedside or in the office would increase the utilization of this important measurement in the routine investigation of the peripheral circulation in patients who are believed or known to suffer from peripheral vascular disease. The cost of the equipment with which to record blood flow by the transistorized DC amplifying system is considerably less than that of commercially available plethysmographs. Repeated determinations of blood flow in the limbs by the mercury-gauge technique vary by less than 10 per cent, and it is anticipated that the system will prove helpful to the practicing physician in the evaluation of therapeutic procedures and of drugs on blood flow in the limbs.

Summary

A mercury strain-gauge plethysmographic system which employs an inexpensive, battery-powered, transistorized DC amplifier and a portable electrocardiographic recorder for the measurement of systolic arterial pressure and blood flow in the limbs is described. The accuracy of the plethysmographic method for determining systemic arterial pressure was demonstrated by comparing it with methods which simultaneously determined direct arterial pressures. The applicability to a variety of clinical problems of both the DC and AC amplifying systems was discussed. The technique has been found to be particularly useful in the preoperative and postoperative study of patients with coarctation of the aorta, in the study of newborn infants and older infants, and in patients of all ages who are in shock or in whom vasoconstriction is marked. It is also anticipated that the plethysmographic system utilizing the transistorized

Further studies on the first derivative of the electrocardiogram, including instruments available for clinical use

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The high-frequency content of electrocardiograms is much greater in subjects with coronary disease than in normal control subjects. This has been demonstrated by methods using high-fidelity electrocardiography,[1,2] power spectrum analysis,[3] and an electronic filter.[4] It has been shown that the detection of high-frequency components, not revealed by the conventional electrocardiogram, may be an adjunct in the diagnosis of coronary heart disease.[2] Recently, the first derivative of the electrocardiogram with respect to time has been employed to display high-frequency components.[5] This method emphasizes rapid rates of change in motion of the original electrocardiogram and thus provides a valuable tool for studying high-frequency components and for distinguishing between high-frequency signals and noise. It is the purpose of this paper to report further observations on the first derivative of the electrocardiogram and to evaluate the adequacy with which it is recorded by several methods, including instruments used in routine clinical electrocardiography.

Material

Ten normal subjects whose high-fidelity electrocardiograms showed complete absence of notching and little or no slurring in 6 or more of the 12 conventional lead axes, and 7 patients whose high-fidelity electrocardiograms contained an abnormal degree of notching and slurring were selected for comparison. Since the signal-to-noise ratio deteriorates markedly after differentiation, the original leads chosen for study must be relatively free of muscle tremor (and 60-cycle interference). In the case of young normal subjects, standard limb leads are often satisfactory but frequently contain enough tremor to be unusable. In these latter cases the standard chest leads are usually adequate. In the case of older patients, and occasionally in some normal subjects, even the standard chest leads contain an excessive amount of tremor. A suitable lead with low level of muscular tremor was found after some experimentation. It consists of one electrode attached to the sacrum and a second to the top of the sternum. This lead gave usable results in all cases studied and was

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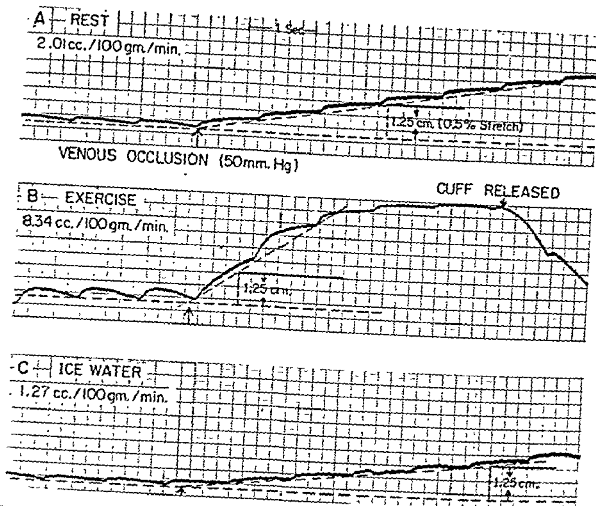


Fig. 12 Recordings of blood flow in the forearm, at rest (*A*), immediately after muscular exercise (*B*), and after immersion of the hand into ice water (*C*).

DC amplifier will simplify the measurement of blood flow in the limbs of patients with peripheral vascular disease.

The authors gratefully acknowledge the advice and cooperation of Dr. H. E. Holling.

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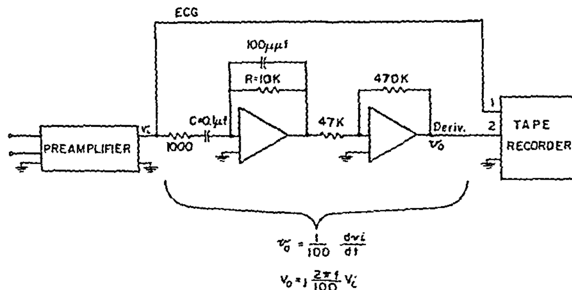


Fig. 1. Circuit diagram showing equipment used in recording data. Triangles are operational amplifiers.

The relationship between the two curves is illustrated in Fig. 4. A simple R wave will result in a biphasic first derivative for the following reasons: There is initially a positive slope in the original electrocardiogram which results in a positive value of the first derivative. Then at the peak of the R wave the slope is zero and the derivative becomes zero, that is, returns rapidly to its base line. After the peak, the original electrocardiogram slopes downward so that the derivative becomes negative. Then as the rate of change in the original electrocardiogram slows down, the first derivative returns upward toward its base line. Each Q, R, or S wave of the electrocardiogram results in a base-line crossing in the derivative. Examples of smooth monophasic, biphasic, and triphasic QRS complexes and their first derivatives are shown in Fig. 4,*A*.

Fig. 4,*B* illustrates different electrocardiograms and the resulting first derivative in the event of notching or slurring. Any distinct notch in the original electrocardiogram will be reflected in the first derivative as an extra biphasic deflection which crosses its base line In Fig. 4,*B*, the first R wave has one notch, the second R wave has two notches, and the third R wave has a slur. Their respective derivatives are shown below The dotted line indicates the portion of the derivative due to the high-frequency component As the drawings in Fig. 4 illustrate, the greatest excursion in the first derivative occurs when the electrocardiogram is showing the greatest rate of change.

Conversely, those portions of the electrocardiogram which have a slow rate of change, e.g., the T wave, will have relatively little influence on the first derivative when compared with the effects of rapid rates of change. An additional discussion of the basic relationships between the electrocardiogram and its first derivative has been presented elsewhere.[5]

Table I. Combinations of paper speed and frequency response selected for detailed study of the first derivative of the electrocardiogram

Paper speed (mm/sec)	*Cutoff frequency (c.p.s.)*	*Equipment*
600	1,000	Dual-beam oscilloscope plus electronic filter plus moving photographic paper
600	600	
350	600	
350	200	
200	600	
200	500	
75	500	Sanborn "Twin Beam"
100	100	Sanborn "Viso 100"
50	100	

used when the standard leads were unsatisfactory.

Procedure

Each lead from each subject used in the experiment was recorded simultaneously with its first derivative on an Ampex FR 1100 magnetic tape recorder at a tape speed of 15 inches per second The derivative was obtained from an electronic network which consisted of two solid-state operational amplifiers (Philbrick P2) with appropriate feedback elements as shown in Fig. 1. Next, a tape loop long enough to display 4 to 6 complexes was made for each lead and played back repeatedly. With the tape loop it is possible to locate and study the same complex by virtue of its relationship to a marker signal such as the splice noise. Fig. 2 shows a typical record of 6 derivatives contained on one loop. In this fashion, beat-to-beat variability is avoided in making comparisons.

The original electrocardiogram and its first derivative from the tape recorder were then filtered and recorded on photographic paper, using different combinations of paper speed and frequency response. A Krohn-Hite filter, Model 330M, was used as a low-pass filter, with a variable upper cutoff frequency response down 3 decibels. After a preliminary survey was made of over 1,000 records to determine where significant changes occurred, several combinations of paper speed and frequency response were selected for detailed study of the first derivative.

The combinations chosen are shown in Table I. The first 6 were obtained by photographing a dual-channel oscilloscope on Linagraph paper, 12.7 centimeters wide, using a high-speed paper transport. The Krohn-Hite filter was used to simulate the frequency response for the derivative. The original electrocardiogram, recorded for reference, was always filtered at 600 cycles per second. In addition, two commercial instruments manufactured by the Sanborn Company were studied as indicated. Here the frequency response was determined solely by the recorder itself.

The "Twin Beam" has a paper speed of 75 millimeters per second. The "Viso 100" was operated at the routinely available speed of 50 millimeters per second, as well as at 100 millimeters per second, which was achieved with a special paper puller designed by the Sanborn Company. Since the "Viso" is a single-channel instrument, records of original and first derivative had to be taken independently. They were matched for phase with the help of the dual-channel recordings.

Differentiating network

To check that the differentiating network was functioning properly, curves of relative amplitude and phase were obtained as a function of frequency. An oscillator was connected to the input of the preamplifier. The input and output signals were then compared on a dual-beam scope with the amplitude adjusted to compensate for the gain of the preamplifier. Results are shown in Fig. 3.

Theoretically, the phase shift should have a constant value of 90 degrees, whereas the amplitude should increase linearly with frequency. On a log-log plot the curve of amplitude versus frequency should be a straight line, with unity slope which has an intercept of 10 times 2π RC at $f = 1$ cycle per second. The factor of 10 is the gain of the inverting amplifier stage; RC is chosen to be 10^{-3}. The amplitude curve follows the theoretical one exactly for low frequencies but begins to fall off markedly above 1,000 cycles per second. The phase curve decreases almost linearly with frequency in the range from 100 to 1,000 cycles per second, corresponding to a time delay of a little less than a quarter of a millisecond. At the maximum paper speed of 600 mm. per second, this delay is equivalent to 0.15 millimeter, which is entirely inconsequential. Hence, for the purposes of the present experiment, the network may be considered to accurately differentiate components to 1,000 cycles per second.

The frequency limitation is actually imposed by the 1,000-ohm resistor in series with C and the 200-ohm output resistance of the preamplifier. This resistance was found to be necessary to insure stability of the circuit.

General principles

The first derivative represents the time rate of change of the original electrocardiogram or its slope at each instant of time.

using a paper speed of 200 millimeters per second and a high-frequency galvanometer is commercially available at a lower cost than the equipment we used. If the frequency response is lowered to 100 cycles per second, the response of the "Viso 100" results in more loss of information in the original electrocardiogram than in the first derivative, and provides less information than the other methods employing a high-frequency response and faster paper speed. There is, however, a modest gain in some information obtained by using the first derivative on the "Viso 100," as compared with the original electrocardiogram made by the "Viso 100."

The record made with the "Twin Beam" presents an interesting combination. The frequency response of the instruments is 500 cycles per second, which is quite adequate, but there is a substantial reduction in paper speed to 75 millimeters per second. Because of the slow paper speed, there is significant loss of notching observed in the original electrocardiogram made on the "Twin Beam," as compared with the records made with expanded time scales, but the first derivative on the "Twin Beam" reveals much more information than the "Twin Beam" electrocardiogram. To evaluate this first derivative, a magnifying glass is required and some practice is necessary, because the deflections with slow paper speed are very close together and often overlap.

The first derivative of the "Twin Beam" contains about 70 per cent of the high-frequency events clearly observable with the expanded time-scale technique. The first derivative of the "Viso 100" gives less than 40 per cent of these events. Regardless of the type of equipment or system used, higher frequency events can be seen more easily in the first derivative than in the original QRS made with the same instrument.

Fig. 7,*A* shows Lead V_3 from a subject with coronary disease. The original electrocardiogram is not remarkable. Its first derivative shows about a dozen deflections that could not be predicted on the basis of the original electrocardiogram. These events are, of course, extremely small but they were repetitive. For comparison, *B* of Fig. 7 shows a normal Lead V_3 and its first derivative, in which there is no additional high-frequency information.

It is common to see variations in respiration cause changes in the QRS in conventional electrocardiography, particularly in limb leads of small amplitude. This is seen to an even greater extent with the high-frequency components of the first

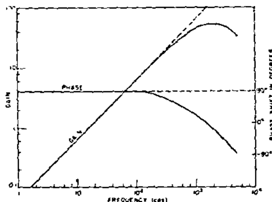


Fig. 3. Experimental curves of gain and phase shift versus frequency for the differentiating network. Ideal curves are shown by dashed lines.

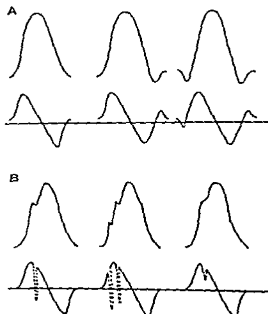


Fig. 4. Illustrative sketches of QRS complexes and their respective first derivatives. *A*, Unnotched complexes. *B*, The results of notching and slurring on the first derivative. The portion of the first derivative affected by the notching and slurring in the original is drawn with dashed lines in the first derivative.



Fig. 2 A strip of the first derivative played back from a magnetic tape loop on a direct writer at the slow paper speed of 25 millimeters per second. The sharp spikes labeled *S*, seen at the beginning and end of the strip, were produced by two successive passes of the tape splice.

Signal versus noise

Noise is rarely a problem in conventional electrocardiography. However, in high-fidelity electrocardiography and in recordings of the first derivative, noise is often quite apparent, and it is vital to distinguish it from signals which originate in the myocardium.[2] One criterion is that the signal must be sufficiently large in comparison with base-line noise. But what is "sufficiently large" is not always obvious (see Appendix I of Reference 2). A second criterion is that the signal be clearly repetitive in successive complexes.

The problem of noise is much more severe in the case of the derivative. In subjects with considerable muscle tremor the first derivative may be dominated by the differentiated noise to such a degree that it is impossible to evaluate the record. The problem may usually be circumvented by using lead systems to minimize tremor, such as the sacrum-to-sternum lead mentioned above or those reported by Abarquez and associates.[6]

Fortunately, the noise is relatively much richer in higher frequency components than the electrocardiographic signals, and considerable improvement in signal-to-noise ratio can be achieved by passing the signal through a low-pass filter. However, if the cutoff frequency is lowered too far, we will begin to lose signal information. Part of the purpose of this paper is to attempt to evaluate the best compromise.

Results

Normal control subjects with leads free from notching or obvious slurring were selected for study. As might be anticipated in such subjects, there were no significant differences in the information obtained by any of the instruments using different combinations of paper speeds and frequency responses, except in the direct-writing instrument, which failed to reveal the high-frequency slurring occasionally seen in the first derivative of normal control subjects.

Results from abnormal subjects with marked notching and slurring are illustrated in Figs. 5 and 6. A paper speed of 350 millimeters per second and a frequency response of 500 to 600 cycles per second were adequate to visualize a vast majority, if not all, of the high-frequency components in both the original and the first derivative. Although considerable information can be obtained from the first derivative when one lowers the frequency response of the system to 400, 300, or 200 cycles per second, high-frequency components which occur in rapid succession will be progressively lost (see Figs. 5 and 6). Decreasing the paper speed results in loss of information through loss of resolution.

The high-fidelity method for the original electrocardiogram with an adequate frequency response (.1 to 600 cycles per second) and a fast paper speed usually reveals the same information seen in the first derivative which is recorded at 500 or 600 cycles per second, although the derivative greatly emphasizes the high-frequency components so that they can be evaluated with greater confidence. Reducing the paper speed to 200 millimeters per second with a frequency response maintained at 500 cycles per second gives essentially the same information as faster paper speeds, but it is more difficult to read. This combination is included because equipment

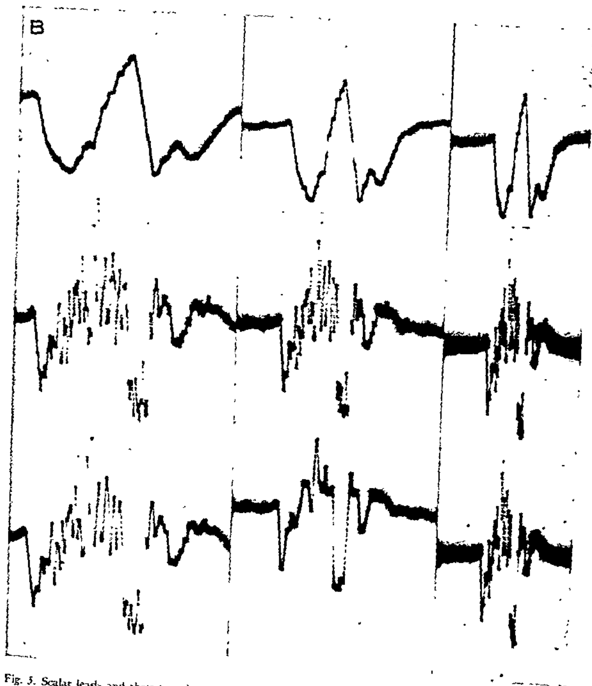


Fig. 5. Scalar leads and their first derivatives from two subjects with healed myocardial infarction. In both instances a lead from the sacrum to the top of the sternum was used to minimize skeletal muscle noise. The arrangement of leads according to paper speed and frequency response is the same for both *A* and *B*. Only the QRS complex is shown. The top row of complexes in each figure are the original high-fidelity electrocardiograms. The next two rows of records are the first derivative of the original electrocardiogram. Paper speeds of 600 millimeters per second, 350 millimeters per second, and 200 millimeters per second, respectively, refer to each vertical column. The upper limit of frequency response in cycles per second for recording the first derivatives in the second horizontal row were 1,000, 600, and 600, and in row three, 600, 200, and 500 cycles per second. Each record was made separately for clarity and lined up in regard to phase with the aid of another two-channel record in which the original electrocardiogram and its first derivative had been recorded simultaneously. Identical QRS complexes could be obtained for each record because a magnetic tape loop was used, as explained in the text. In the 200 cycle record there is obvious loss of significant fluctuations in the first derivative caused by lowering the frequency response. For further explanation

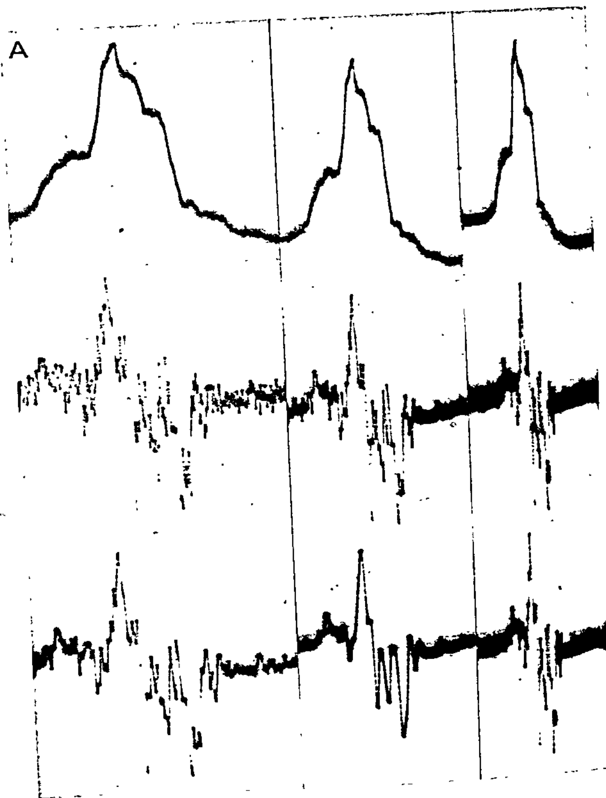


Fig. 5,A. (For legend see opposite page.)

derivative. There may be considerable beat-to-beat variation, particularly in the smaller, very fast deflections. At a given beat of the respiratory cycle, however, the form of the first derivative will be practically identical with that recorded at the same phase of subsequent respiratory cycles. The technique of the tape loop is useful for either eliminating beat-to-beat variation or for studying its effect.

Discussion

The results have shown that high-frequency components distinctly revealed in the original high-fidelity electrocardiogram are emphasized in its first derivative. The original electrocardiogram must, of necessity, contain all the high-frequency components seen in its first derivative, but at times these components may be difficult to read or to evaluate with complete confidence, and at times they are obscured in the electrocardiogram as compared to its first derivative.

The subjects studied were normal ones with smooth, unnotched leads, and abnormal ones with obvious and marked notching. It should be emphasized that any given notch which occurs in the electrocardiogram may have the same physical properties whether the subject is normal or abnormal, and, therefore, has the same

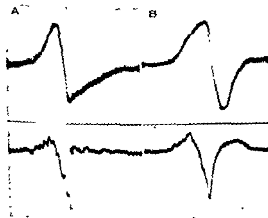


Fig. 7. *A*, Shows Lead V_2 from a subject with healed myocardial infarction. The first derivative, mounted below, reveals additional information. *B*, Lead V_2 (*above*) and its first derivative (*below*) from a normal control subject. In each record the paper speed is 350 mm. per second, the frequency response is 1 to 600 cycles per second.

effect on the first derivative. The difference between a majority of abnormal subjects and normal control subjects is that the former may have much more notching, and, therefore, have more fluctuations in the first derivative. In both normal and abnormal subjects a substantial level of skeletal muscle noise or power-line interference will make the reading of the first derivative record difficult, if not impossible.

Filtering of the derivative is a practical necessity because with a frequency response of 1,000 cycles per second or higher the amplitude of the differentiated noise interferes with the reading of the signal. Fortunately, as one reduces the frequency response, the amplitude of the noise is reduced more than the amplitude of the signal (see Figs. 5 and 6). For the abnormally notched records which were deliberately chosen for study here, a frequency response to 500 or 600 cycles per second seems to provide a reasonable compromise.

When operating at a gain so that the amplitude of the largest deflection of the first derivative is comparable to the amplitude of the QRS in the high-fidelity electrocardiogram, one usually sees no deflections in the first derivative at the site at which the T wave occurs in the original electrocardiogram because the T wave contains very low frequency components (see Fig. 6,*A*). Usually, small deflections are seen in the first derivative of the P wave (see Fig. 6,*B*). In order to see the first derivative of the P and T complexes of body surface leads, it is usually necessary to use a low-pass filter set at about 20 to 30 cycles per second, which eliminates all but the very low frequency components of the electrocardiogram. The QRS complex, of course, will be grossly distorted.

Another possible use of the first derivative is suggested by the high percentage of notching in the original electrocardiograms of abnormal subjects reported elsewhere.[2] In the high-fidelity electrocardiograms of the abnormal subjects there was a much greater incidence of notching than in those of the normal control subjects. However, in some of the subjects in both the normal and abnormal groups there were leads with a borderline number of

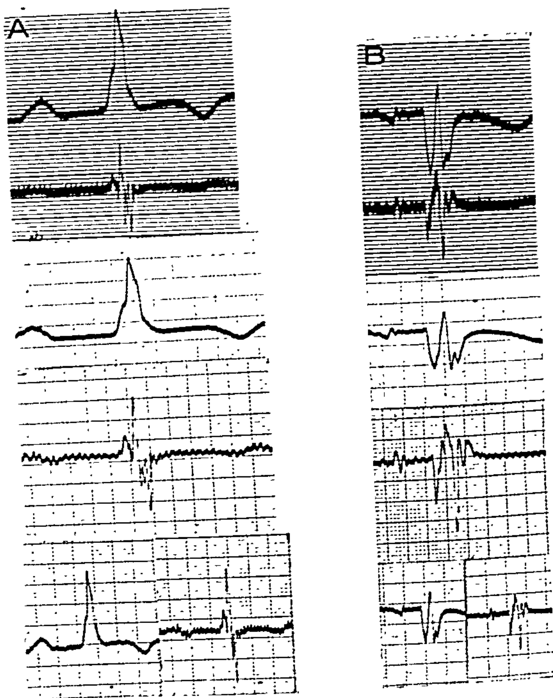


Fig. 6. Records from the same subjects as in *A* and *B* of Fig. 5. The top pair of records are two-channel "Twin Beam" recordings of the electrocardiogram and its first derivative. Next there is a "Viso 100" recording of the original electrocardiogram, and below this is its first derivative at a paper speed of 100 millimeters per second. On the bottom row, side by side, are "Viso 100" recordings of the original and its first derivative at a paper speed of 50 millimeters per second. As explained in the text, information is lost as compared to the results shown in *A* and *B* of Fig. 5

Persistent electrocardiographic abnormalities experimentally induced by stimulation of the brain

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Abnormal electrocardiographic findings which led to the diagnosis of myocardial ischemia and infarction have been reported to occur in the absence of organic heart disease in patients suffering from severe neurological disorders. Levine,[1] in 1953, reported such a case in which there was subarachnoid hemorrhage from an aneurysm of the circle of Willis, but careful examination failed to reveal pathologic findings in the heart. Burch and co-workers[2] reported a series of 17 patients afflicted with cerebrovascular accidents in whom irregularities of the electrocardiogram developed. Wasserman and associates[3] reported that changes in the electrocardiogram followed soon after the onset of acute cerebrovascular accidents although most of their patients had clinical evidence of organic heart disease. More recently, Gropp and Manning[4] studied 29 cases of subarachnoid hemorrhage and found signs suggestive of recent myocardial ischemia or infarction in 15. Four of their patients who died exhibited normal hearts at autopsy. The most prominent findings in these series have been alterations in the T wave, deviation of the S-T segment, and prolongation of the Q-T interval.

In other series, irregularities in the electrocardiogram have been reported to occur in patients with a variety of lesions of the central nervous system,[5] and occasionally in children suffering from encephalitis.[6] It is the purpose of this communication to report the occurrence of persistent electrocardiographic changes of a similar nature which followed electrical stimulation of the brain in 7 cats.

Methods

These acute experiments were performed in unanesthetized male and female cats which weighed 2 to 4 kilograms. The animals were first anesthetized with ether to allow for the necessary minor surgical operations. Tracheal intubation was done to facilitate artificial respiration. Cannulations of the femoral artery and vein were performed to enable monitoring of the blood pressure and for injection of drugs, respectively. A small craniotomy was made to allow the insertion of stimulating electrodes stereotactically into the brain. In 3 experiments a laminectomy was performed so that the spinal cord might be transected later in the experiment. Electrocardiographic leads were taken from the right

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notches. Further study is indicated to determine whether the first derivative, by revealing latent slurs, would be helpful in distinguishing between such normal and abnormal subjects with borderline records.

Summary and conclusions

The first derivative of the electrocardiogram with respect to time greatly emphasizes the high-frequency components which are clearly visible in the original high-fidelity electrocardiogram so that they can be read with a high degree of confidence. In addition, in some individuals the first derivative reveals high-frequency components which are not readily apparent in the original high-fidelity electrocardiogram.

A system with a frequency response which is adequate from .1 to at least 500 cycles per second is necessary for the study of high-frequency components in both the original electrocardiogram and its first derivative. With lower frequency responses, information is progressively lost. The optimum paper speed for clear visualization was 350 millimeters per second. With an upper frequency response of 500 cycles per second, a paper speed of 200 millimeters per second provided all the information present, but the record was somewhat more difficult to read.

Two conventional instruments were studied. Both gave less information than either the original high-fidelity electrocardiogram or its first derivative. In the case of one conventional instrument the first derivative gave considerably more high-frequency information than did the original electrocardiogram made with the same instrument.

Differentiated noise is frequently a serious problem in the evaluation of records of the first derivative, and measures to minimize this have been discussed. The results suggest that the first derivative of the electrocardiogram with respect to time is worthy of further study, in order to determine how much additional information it will yield that cannot be appreciated by simple inspection of the original high-fidelity electrocardiogram.

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were verified histologically. Extensive gross and microscopic examinations of the heart were performed.

Results

All 7 of the animals described in this report showed abnormalities of the electrocardiogram which were at first transient on stimulation of the brain but then became permanent either spontaneously or after repeated cerebral stimulation. Alterations in the electrical pattern were noted from 10 to 20 seconds after the beginning of stimulation of the brain. Initially, they developed over a period of several seconds and persisted for as long as several minutes. The duration of the abnormal cardiac changes could not be correlated with the duration of the cerebral stimulation. After the second or third period of stimulation these changes became persistent, if they were not already so.

The most consistent findings in the electrocardiogram included inversion and increased amplitude of the T wave, prolongation of the Q-T interval, and deviation of the S-T segment. In other experiments, ventricular extrasystoles, either singly or in short trains, were encountered when similar cerebral sites were stimulated (unpublished data). Fig. 1 shows the effect of a 20-second period of stimulation of the ventral hippocampus. In this example the maximum effect is noted in *B*, which shows an inversion and increase in the amplitude of the T-U wave. The duration of the Q-T interval is lengthened, and at the height of this effect it appears to be encroaching upon the beginning of the P wave. The take-off of the S-T segment is slightly elevated in this example. In this experiment the cardiac abnormalities began to disappear as the tracing returned to normal approximately 12 seconds after cessation of the stimulus. The gradual decrease in the amplitude of the T waves can be noted in *C*. Within 30 seconds after cessation of the stimulus the electrocardiogram resembled closely the control tracing (*D*).

The effect of a second period of stimulation (15 seconds) delivered to the brain 20 minutes after the first one described above is shown in Fig. 2; similar changes in the pattern of the T wave have developed (*B*). On cessation of stimulation, however, no change in the electrocardiographic pattern occurred. Two hours later the general pattern of electrical activity was similar, although the rate had diminished. (Under the conditions of these experiments the heart rate of the cat initially averaged between 170 and 220 beats per minute.)

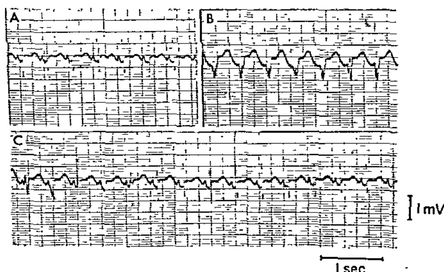


Fig. 3. Effect of transection of the cervical spinal cord upon the persistent electrocardiographic abnormalities induced by cerebral stimulation. *A*, Control tracing before stimulation. *B*, Tracing 2 hours after cessation of stimulation of the brain. *C*, Ten seconds after the transection of the cervical spinal cord.

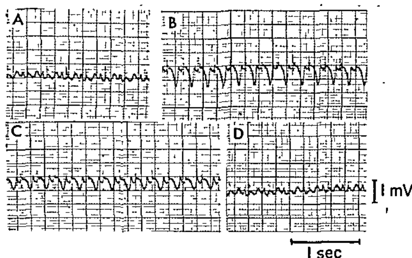


Fig. *1*. Transient electrocardiographic changes induced by initial period of stimulation. *A*, Control tracing. *B*, Maximal effect manifested 15 seconds after beginning of stimulation. *C*, Tracing 15 seconds after cessation of stimulus. *D*, Tracing 30 seconds after termination of cerebral stimulation.

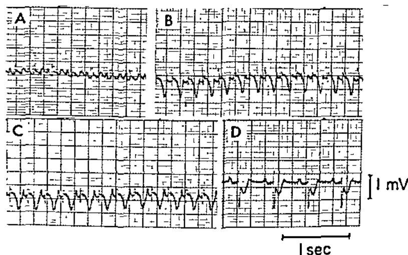


Fig. *2* Electrocardiographic changes induced by the second period of cerebral stimulation *A*, Control tracing. *B*, Tracing taken 15 seconds after the start of stimulation of the ventral hippocampus. *C*, Tracing taken 2 hours after cessation of stimulation. *D*, Persistent electrocardiographic changes 4 hours after termination of stimulation.

forelimb, which was stretched out in front of the animal, and from the left hind limb. Tracings were made on a Sanborn electrocardiograph. All wound margins and pressure points were infiltrated with 1 per cent procaine. Flaxedil (gallamine triethiodide, 1 c.c.) was given intravenously, and artificial respiration was instituted. At least 2 hours were allowed for the effects of the ether to wear off before stimulation of the brain was started. Stimulation of the brain was effected with a biphasic pulse from a Grass square-wave generator (stimulus parameters: .8 milliampere; 3 to 10 volts; 1.0 to 3.0 milliseconds pulse duration; 100 pulses per second; 15 to 30 second train duration). At the termination of experiments the electrode placements in the brain

genically induced changes were allowed to run their course, complete heart block and, eventually, ventricular fibrillation resulted.

It has been known for many years that transient alterations in the configuration of the T wave, as well as ventricular extrasystoles occur during stimulation of the brain. Beattie and associates[7] have shown that the integrity of the posterolateral hypothalamus was necessary for the occurrence of ventricular extrasystoles under light chloroform anesthesia. Previously, Levy[8] had reported that, under these conditions of anesthesia, extrasystoles were apt to occur spontaneously or could be induced with Adrenalin or stimulation of the sciatic nerve. More recently, Weinberg and Fuster[9,10] have demonstrated that the neurogenic origin of such ventricular abnormalities is not dependent upon anesthesia but can be produced with considerable regularity under certain parameters of electrical stimulation. They, too, found that the posterolateral hypothalamus was the area from which such changes could be elicited. In addition to the persistent changes induced by repeated stimulation of the structures of the medial temporal lobe, as noted in this report, we have also been able to induce transient electrocardiographic changes by stimulating the posterolateral hypothalamus (crosshatched circle in Fig. 4).

The peripheral mechanism through which such neural discharge elicits abnormalities in the electrical patterns of the heart can only be speculated upon. Possibly through the intermediation of sympathetic pathways a ventricular focus is established which at times may be irritative in nature, leading to ventricular extrasystoles, and which at other times may show impairment of repolarization, leading to the appearance of electrocardiographic changes which simulate myocardial ischemia. Although the immediate return of the electrocardiogram to normal on removal of neural influences, and the absence of microscopic changes in the myocardium suggest the functional nature of this phenomenon, the fact that it may lead to irreversible cardiac dysfunction, at least under experimental conditions, is emphasized.

Summary

Persistent abnormalities in the electrocardiogram have been induced by stimulation of the ventral hippocampus and the medial nuclei of the amygdala. Most frequently seen were inversion and increased amplitude of the T wave, deviation of the S-T segment, and prolongation of the Q-T interval. These changes were transient during the first period of stimulation but became persistent after subsequent stimulation. Transection of the cervical spinal cord caused the disappearance of these abnormalities and a return of the electrocardiogram to its prestimulation state.

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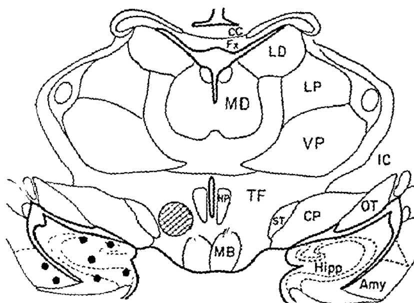


Fig. 4. Sites of stimulation in the medial temporal lobe which induced electrocardiographic changes. *CC:* Corpus callosum. *Fx:* Fornix. *LD:* Nucleus lateralis dorsalis. *MD:* Nucleus medialis dorsalis. *LP:* Nucleus lateralis posterior. *VP:* Nucleus ventralis posterior. *TF:* Tegmental fields. *HP:* Nucleus hypothalamicus posterior. *MB:* Mammillary body. *ST:* Subthalamus. *CP:* Cerebral peduncle. *IC:* Internal capsule. *OT.* Optic tract. *Hipp:* Hippocampus. *Amy:* Amygdala. (According to Jasper, H. H., and Ajmone-Marsan, C.: A Stereotaxic Atlas of the Diencephalon of the Cat, Ottawa, The National Research Council of Canada.)

At the end of 4 hours the rate was down to 140 (*D*). In this experiment, at the end of the eighth hour the cat had developed complete heart block with idioventricular rhythm, and within 2 more hours it manifested ventricular fibrillation. An additional 3 animals developed this same pattern of cardiac events within 6 to 10 hours.

In the other 3 animals, transections of the spinal cord were performed at varying times after the onset of similar persistent electrocardiographic abnormalities. Fig. 3 shows the effect of transection of the cervical spinal cord 2 hours after the onset of abnormal ventricular function. Ten to 15 seconds after the cord had been transected, the electrocardiogram returned to essentially the prestimulation state (*C*). In the other acute experiments the spinal cord was transected progressively in a cephalad direction through the thoracic region, but no alteration of this centrally induced cardiac irregularity was observed until the mid-cervical region was cut. Similarly, in these experiments the time required for return to the control state ranged between 10 and 15 seconds after the cervical cord had been sectioned.

The areas of the medial temporal lobe which when stimulated induced electrocardiographic changes are indicated in Fig. 4. These loci are in the hippocampal formation (dentate gyrus, subiculum, and hippocampal gyrus) and the medial nuclei of the amygdala.

Examination of the hearts of these animals failed to reveal any significant abnormalities.

Discussion

These animal experiments are of interest in that transient stimulation of the brain resulted in persistent abnormalities of the electrocardiogram which were similar in many respects to those which occur as a consequence of severe brain disease. The fact that transection of the cervical spinal cord eliminated these abnormalites in 3 animals suggests the existence of a tonic neural discharge which outlasts the duration of the stimulus by many hours. In the other 4 animals in which these neuro-

Laboratory findings. The urinalysis revealed 20 to 30 hyaline casts with a rare red blood cell, 0 to 2 white blood cells, and a moderate number of bacteria. Specific gravity was 1.014, with a pH of 4.5. Serum chlorides were 91 mEq. per liter, carbon dioxide 23.9 volumes per cent, serum sodium 136 mEq. per liter, potassium 3.8 mEq. per liter, calcium 9 mg. per cent, and serum transaminase after admission was 50 units. The hemoglobin was 13.4 Gm. per cent, the white blood cell count was 9,600 per cubic millimeter, and the hematocrit was 41 per cent. The differential count showed 84 per cent polynuclear neutrophils, 1 per cent nonsegmented neutrophils, 2 per cent eosinophils, 1 per cent basophils, 5 per cent lymphocytes, and 7 per cent monocytes. There were macrocytes, microcytes, target cells, polychromatophilia, anisocytosis, and poikilocytosis present in the smear. The rapid sickling test was negative. Fasting blood glucose was 112 mg. per cent, blood urea nitrogen 50 mg. per cent, serum creatinine 1.6 mg. per cent, and serum uric acid 13 mg. per cent. An ECG taken on the day of admission revealed atrial flutter with a 2:1 atrioventricular conduction and occasional premature beats. Contour alteration suggestive of an anterolateral wall infarct was found. The portable chest x-ray film revealed cardiomegaly with vascular congestion.

Hospital course. The patient was treated with Cedilanid, Mercuhydrin, oxygen, and aminophylline. Intramuscular heparin was administered every 6 hours the first day, and procaine penicillin, 600,000 units daily. Dicumarol therapy was started on the second hospital day. The ECG on the second day again showed atrial flutter. The ischemic pattern had failed to evolve as that of a recent infarction. On the third day the patient's rhythm was that of atrial fibrillation with an average ventricular rate of 75 and runs of ventricular ectopic beats, for which potassium was administered. Further laboratory work showed a transaminase of 46 and 30 units. Serum cholesterol was 100 mg. per cent, with 69 per cent esters. Carbon dioxide was 22.8 volumes per cent, pH was 7.46, serum sodium was 134 mEq. per liter, and potassium was 4.9 mEq. per liter. The blood urea nitrogen on the sixth day of hospitalization was 96 mg. per cent, and the creatinine was 1.6 mg. per cent. A study of the blood on the seventh day showed a hemoglobin of 12.7 Gm. per cent, with a hematocrit of 40 per cent and a white blood cell count of 14,000 per cubic millimeter, with 67 per cent polynuclear neutrophils, 1 per cent eosinophils, 20 per cent lymphocytes and 12 per cent monocytes. A protein-bound iodine was within normal limits.

The patient died suddenly on February 14, at 8:40 in the morning.

Discussion

DR. SILBER: The problem for the clinician is to determine the nature of the heart disease with which this patient was afflicted, and to assign the proper precipitating cause of death.

The finding of an elevated diastolic (and systolic) blood pressure during the first hospitalization, together with the history of "high blood pressure for many years" establishes the diagnosis of hypertension, but not necessarily that of hypertensive heart disease. The modest level of elevation and the "empty" urine seem to deny a pyelonephritic etiology so commonly found in the American Negro. The finding of a huge prostate at the age of 52 points to an obstruction of the lower urinary tract as a likely cause. No inventory of symptoms is present in the protocol to confirm or deny these suspicions. It is clear, however, that the patient suffered none of the direct cardiorenal complications of hypertension.

If we turn our attention now to the cardiac murmur described during the first hospitalization, it is evident that we cannot assign such a bruit simply to the hypertension which exists, nor, from the description, does it appear to be the murmur of aortic stenosis, interventricular septal defect, or aortic dilatation. Despite the absence of a history of rheumatic fever (a not uncommon circumstance), the characteristics of the murmur, together with the radiographic and electrocardiographic findings of the first hospitalization, make mitral insufficiency the most reasonable basis for this abnormal physical finding.

It is my belief that at the conclusion of the first hospital admission the patient had hypertension secondary to disease of the lower urinary tract and, in addition, rheumatic mitral valvulitis with insufficiency. Both, as laboratory studies reveal, have had a dynamic effect on the heart, but were, at the time, asymptomatic.

Nine years later, at the time of the second hospitalization, we learn that the disease had made significant inroads upon the reserves of the heart. There was a history of several years of dyspnea, which was acutely intensified 5 days before admission. Moreover, at the time the patient was admitted to the hospital, he was in frank congestive heart failure. Was all of this on the basis of the valvular heart disease and hypertension, or was there another basis for the break in compensation? The key to this answer lies, I believe, in the electrocardiograms. I and Dr.

Clinical pathologic conference

Earl Silber, M.D.
Alfred Pick, M.D.
Dorothy E. Eshbaugh, M.D.
Chicago, Ill.

Clinical abstract

First admission (Oct. 27 to Nov. 12, 1952) This 52-year-old Negro man entered Michael Reese Hospital for repair of bilateral inguinal hernias, which were found 1 month before admission by a company doctor. The patient had no symptoms referable to the hernias, and both were easily reduced.

Past history. The patient gave a history of hypertension several years prior to admission. There was no history of rheumatic fever, and no shortness of breath, wheezing, or peripheral edema. There was a history of indulgence in alcohol over many years.

Physical examination. Blood pressure was 196/110 mm. Hg, pulse was 100, respirations were 28 per minute. Bilateral arcus senilis and opacities of both lenses were found. The fundi were not well visualized. There was no venous engorgement. Examination of the lungs revealed moist expiratory and inspiratory râles in both bases. A questionable friction rub was heard over the left side of the chest by one observer. The heart was enlarged, and the point of maximal impulse was felt at the left anterior axillary line, the border of the left heart was percussed at that point also. There was a regular rhythm with a Grade 3 systolic murmur over the entire precordium, heard best at the apex, and transmitted to the axilla. The border of the liver was felt 2 fingerbreadths below the right costal margin. Both inguinal rings were dilated. The rectal examination revealed a Grade IV prostatic enlargement. No edema or varicosities were found in the extremities.

Laboratory findings. The blood urea nitrogen was 14.5 mg. per cent, with a fasting blood sugar of 80 mg. per cent, serum creatinine was 1 mg. per cent. Creatinine clearance was 78 c.c. per minute. Urinalysis was essentially negative except for 1+ albumin. The complete blood count as well as the liver function tests were well within normal limits. A chest x-ray film was read as suggestive of left atrial, left ventricular, and right ventricular enlargement. The ECG showed broad P waves in the limb leads and a first-degree atrioventricular block.

Hospital course. The patient was digitalized and underwent a bilateral herniorrhaphy. Except for a 4-day bout of fever with a temperature that reached 102°F., the patient had an uncomplicated course. He was treated at that time with penicillin.

Second admission (Feb. 7, 1961) The patient entered Michael Reese Hospital at this time with a chief complaint of shortness of breath. He gave a history of several years of heart disease with dyspnea and one questionable episode of pulmonary edema. For 4 weeks prior to hospitalization the shortness of breath had increased. Five days prior to admission his wife was called to take the patient home from work because of severe dyspnea and weakness. He had been in bed since that time, using two pillows for sleeping. He denied paroxysmal nocturnal dyspnea, hemoptysis, cough, fever, peripheral edema, or chest pain.

Physical examination. Blood pressure was 120/96 mm. Hg; pulse was 135 (regular), respirations were 24 per minute, temperature was 100.6°F. rectally. The patient was a well-developed, well-nourished, obese Negro man in moderate dyspnea. He was rather apathetic. Examination of the eyes revealed pin-point pupils, and the fundi could not be visualized. The neck veins were not particularly distended but appeared to be prominent. Crackling râles were heard in the lower half of the left lung field and at the base of the right lung. There was dullness to percussion with increased breath sounds in the same regions. The border of the left heart was percussed at the anterior axillary line. The point of maximal impulse was palpable in the sixth intercostal space at the anterior axillary line, with a suggestion of a thrill. No pulse deficit was present. A Grade 1 systolic murmur was heard at the apex. The liver reached 4 to 5 fingerbreadths below the costal margin and was smooth and tender. The spleen was not palpable. There was no peripheral edema, but 1+ sacral edema.

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(Fig. 2, on Feb. 8, 1961), there was atrial flutter with a 2:1 ventricular response, disturbed by premature ectopic beats with fixed coupling, apparently ventricular in origin. On February 11 (Fig. 2, bottom strip), consequent to digitalization, this changed to atrial fibrillation with a slow ventricular response, and the ectopic beats had disappeared. The alterations in contour which remained stable in seven consecutive electrocardiograms taken over a period of 1 week were as follows (Fig. 2, on February 11): In the limb leads, QRS is now of smaller voltage, markedly slurred, with distinct Q waves in Leads I and aV_L, in association with abnormal ST-T (of digitalis type) in Leads II, III, and aV_F. In the precordial leads, QRS is notched and mainly inverted, with prominent Q waves and small R waves in Leads V_1 to V_3 and a QS configuration in Leads V_4 to V_6. The T waves, however, show no abnormalities over the precordium.

In evaluating these profound alterations

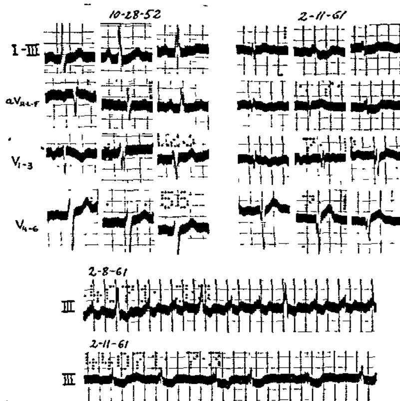


Fig. 2 See text

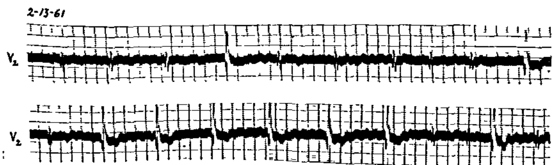


Fig. 3. See text



Fig. 1. See text.

have examined the tracings recorded at the time of the second admission, and I am satisfied that they are indicative of a recent anterolateral infarct. The long-standing hypertension, the age, obesity, sex, and age of this patient, as well as the ethnic group to which he belongs, certainly provide an adequate background for the development of coronary atherosclerosis. Although chest pain is lacking here for the diagnosis of myocardial infarction, such is apparently the case in from 3 to 5 per cent of all instances of myocardial infarction. This percentage is said to be higher in the Negro, for reasons which are obscure. It is well recognized that the abrupt onset of dyspnea and weakness, without pain, may usher in myocardial infarction.

Before turning to the immediate cause of death, I should like to hear from Dr. Gemell and Dr. Pick in regard to the chest x-ray films and electrocardiograms.

DR. GEMELL: A portable chest film is available. We see a rather large heart, with the left side of the heart reaching the chest cage. The pulmonary vascularity is markedly increased. The configuration suggests left as well as right ventricular enlargement, perhaps predominantly right. It is impossible to estimate the size of the atria, especially of the left atrium because of the portable technique. On the basis of the x-ray films, the configuration of the heart and the vascularity of the lungs could be compatible with mitral heart disease or a left-to-right shunt with resulting changes. (See Fig. 1.)

DR. SILBER: In looking at these films, I am struck by three features which are inconsistent with hypertensive and arteriosclerotic heart disease: the aorta is not ectatic, the cardiac enlargement is globular rather than presenting the typical elongated ventricular salient of left ventricular dilatation, and, finally, the pulmonary arteries are strikingly enlarged. Such pulmonary arteries are seen in long-standing mitral valvular disease, congenital lesions associated with left-to-right shunts, or with poststenotic dilatation of the pulmonary artery, and in essential pulmonary hypertension. The available evidence supports only the first possibility, namely, mitral valvular disease. Dr. Gemell, how do you feel about this?

DR. GEMELL: Again, I would like to emphasize that one would have to bear in mind that, because this is a portable film, some degree of distortion is always present. Nevertheless, I would have to agree with Dr. Silber inasmuch as there is certainly no aortic ectasia, as far as one can see. Also, I believe that we all agree that there are no typical changes to indicate only left ventricular enlargement as the predominant feature.

DR. SILBER: Dr. Pick, would you discuss the electrocardiograms?

DR. PICK: The electrocardiogram at the time of the first hospital admission (Fig. 2, on Oct. 28, 1952) shows a sinus rhythm at a rate of 78, with a slight delay in atrioventricular conduction (P-R, 0.22 second). The P waves are large, notched, and broadened (0.14 second), upright in Leads I to III and inverted in Lead V_1. The configuration of the ventricular complexes is normal, except for some slurring of QRS in all leads. This record, therefore, suggests enlargement of the atria, predominantly the left atrium, but there is no evidence of pathology involving the ventricles.

At the time of the second hospital admission, significant alterations were noted in rhythm as well as in contour. At first

DR. ESHBAUGH: At necropsy, the only significant external finding was a moderate pitting edema of the lower legs and over the sacrum. There was no excessive abdominal or pleural fluid. The most significant findings were in the heart and in the lungs.

The heart weighed 650 grams and was markedly dilated, particularly the right atrium and the right ventricle, which measured 3 and 5 mm., respectively. At least two independent pathologic entities were present. There was a large recent myocardial infarct which occupied the anterior two thirds of the interventricular septum and the anterior wall of the left ventricle. The infarct was estimated to be several days old, possibly 5 to 7. The infarct was found adjacent to an organizing infarct. There were small mural thrombi over the infarct in both the right and left ventricles. The coronary arteries were markedly atherosclerotic, and there was a recent thrombus of the anterior descending branch of the left coronary artery, beginning at its origin and extending for a distance of 4.8 cm.

The most outstanding finding, however, was a large atrial septal defect replacing the foramen ovale, which measured 2.6 cm. in diameter. The main pulmonary artery and its larger branches were very markedly dilated. They showed no atherosclerotic changes. The pulmonary valve and the artery above it measured 11.5 cm. in circumference. The left atrium was slightly dilated, and the mitral valve measured 12 cm. in circumference. It showed a moderate thickening and fibrosis of the posterior cusp, with some shortening and thickening of the chordae tendineae. However, the lesion did not appear to be extensive enough to have produced any incompetence and there was certainly no stenosis of the mitral orifice. (See Fig. 4.)

There was a moderate hypertrophy of the wall of the left ventricle, attributable to the arterial hypertension. Grossly, there were no pulmonary emboli or thrombi There was a small amount of pulmonary edema. There was a chronic passive hyperemia of the liver.

The kidneys were of the usual size: each weighed 150 grams. They were the seat of arteriolonephrosclerosis. ɪ ˑ prostate gland was not markedly enlarged or nodular, and there was no evidence of obstruction of the urinary tract.



Fig 6 Pulmonary arteriosclerosis Hematoxylin and eosin preparation, ×295.

Other findings were a chronic cholecystitis and cholelithiasis. An entirely unsuspected finding was a polypoid carcinoma of the stomach. The carcinoma was located in the pyloric region of the stomach and measured 12 cm. in greatest diameter. It was not ulcerated and had produced no pyloric stenosis, which may account for the apparent absence of symptoms. An unusual feature of the tumor was that it extended grossly for a few centimeters into the duodenum.

Microscopic study. The myocardium disclosed large areas which showed necrotic muscle fibers with no recognizable nuclei. The fibers had lost their cross striations, and their cytoplasm appeared to be deeply eosinophilic. In some of these regions there was infiltration with polymorphonuclear leukocytes. In other areas, accumulations of macrophages were present, many of which disclosed abundant vacuolar cytoplasm. Proliferation of fibroblasts was noted in some areas, combined with a new formation of many small-sized ...



Fig. 4. View of left atrium. Note large atrial septal defect and thickening of posterior cusp of mitral valve.

in contour, I think first of an extensive anterior and lateral wall infarct, and the stability of serial tracings would indicate that this infarct is old and healed. However, we have seen records of this type in the absence of myocardial infarction, when marked right ventricular hypertrophy causes clockwise rotation of the heart. Taking into account the long-standing signs of atrial pathology, the atrial arrhythmias, and the clinical and roentgenographic findings, we must consider mitral valvular disease as another distinct possibility.

The last record on February 13 (Fig. 3) is of interest because it indicates a possible cause of death. It shows (in Lead V_2) at first occasional, and later predominant, ventricular complexes that are larger and wider (QRS, 0.12 second) than those transmitted from the fibrillating atria. The long intervals between such beats are multiples of the (slightly irregular) short cycles that can be measured when such beats occur in sequence. It appears, therefore, that on this day a parasystolic ventricular focus was in action, with an intermittent exit block. On the assumption that the actual discharge rate of this ectopic center was even more rapid, and that its exit block was suddenly completely released, a ventricular paroxysmal tachycardia may have been the terminal fatal event in this patient.

DR. SILBER: Since Dr. Pick has now reversed himself and casts serious doubt on the electrocardiographic diagnosis of recent myocardial infarction, he and I have reached a parting of the ways. I will stand by the diagnosis of myocardial infarction.

I would conclude that the patient suffered from long-standing hypertension associated with obstructive disease of the lower urinary tract, that he had rheumatic heart disease with an old mitral valvulitis characterized by dynamic mitral regurgitation, and, finally, that he suffered a myocardial infarct 5 days prior to admission to the hospital.

It remains only for me to assign an immediate cause of death. In circumstances such as these, death could have been due to the development of ventricular tachycardia and fibrillation which was preceded by the observed intermittent ectopic rhythm. Of course, death could have been precipitated by pulmonary embolism, ventricular rupture, extension of the recent infarct, or development of a new coronary thrombosis. With the information available, this can only be a guessing game. Playing it statistically, I will cast my lot with the latter diagnosis. I rest my case and await the pathologist's verdict.

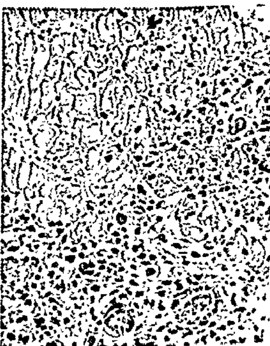


Fig. 5. Recent myocardial infarct adjacent to organizing infarct. Hematoxylin and eosin preparation, ×295.

sociated with cases of atrial septal defect, and sometimes results in mitral stenosis with Lutembacher's syndrome, in this case the involvement of the mitral valve was rather slight and there was definitely no stenosis of its orifice. Whether or not the old mitral valvulitis was actually the result of a previous rheumatic fever cannot be stated with certainty, but seems most likely. Uncomplicated intra-atrial septal defects are often well borne into senescence, as suggested by this case. The apical murmur and thrill reported clinically were apparently due entirely to the atrial septal defect.

Another very important finding in this case was a primary carcinoma of the stomach which seemingly had not produced any clinical symptoms. However, the carcinoma had caused the appearance of multiple small and large emboli in branches of the pulmonary artery. These emboli, in turn, had caused the formation of adjacent fibrin and hyaline thrombi. This and the marked pulmonary arteriosclerosis seem important with regard to the explanation of circulatory dynamics in the lungs.

The hypertension of this patient may very well have been the result of the arteriosclerosis of the kidneys.

The final pathologic diagnoses were: large atrial septal defect (open foramen ovale); dilatation of the pulmonary arteries; recent thrombus in the anterior descending branch of the left coronary artery; recent myocardial infarct involving the anterior portion of the left ventricle and the neighboring septum, with adjacent organizing infarct old endocarditis (slight) of the mitral valve; hypertrophy of the heart; primary adenocarcinoma of the stomach; multiple tumor emboli in branches of the pulmonary artery; pulmonary sclerosis of smaller branches.

In summary, this was a 61-year-old Negro man who had a large congenital intra-atrial septal defect of the heart of the foramen ovale type. He gradually developed hypertension, coronary atherosclerosis with recent thrombosis, and a fresh myocardial infarct. In addition, he had a primary latent adenocarcinoma of the stomach which had produced multiple emboli, with consequent thrombi in many branches of the pulmonary artery. There was also severe pulmonary arteriosclerosis.

DR. SILBER: It is interesting, in retrospect, that the patient actually had three lesions which were consistent with the ECG pattern: (1) interatrial septal defect, (2) obstructive type of pulmonary hypertension, and (3) myocardial infarction. In view of the autopsy findings, it is warranted to attribute the ECG pattern to the latter disease. The chest x-ray film alerted us to a cardiac diagnosis other than that of arteriosclerotic heart disease alone, but we stubbed our toes on mitral valvular disease rather than atrial septal defect. I would not even now attribute the apical murmur to the atrial septal defect. The point that lesions which produce left-to-right shunts, especially atrial septal defect, may be occult in adults and the aged is well illustrated by this patient.



Fig. 7 Carcinoma cell embolus with hyaline thrombus in branch of pulmonary artery. Hematoxylin and eosin preparation, ×225

Many other muscle fibers were obviously hypertropic, with rectangular, blunt-edged nuclei. Both the right and left endocardial surfaces of the septum showed a recent thrombus, which was composed of fibrin, polymorphonuclear leukocytes, and red blood corpuscles with early signs of organization. Sections of the coronary arteries revealed a recent thrombus superimposed on the intima of an atherosclerotic vessel. (See Fig. 5.)

Microscopic sections of the lung showed some unexpected findings. In many areas there was marked thickening of the walls of the larger arteries, and expecially of the smaller ones. Some of the smaller branches of the pulmonary arteries contained carcinoma cells similar to those described below. In addition, there were small and larger thrombi adjacent to these tumor cells. A number of blood vessels were completely occluded by a combination of carcinoma cells and thrombi. Other sections showed evidence only of chronic passive hyperemia. (See Figs. 6, 7, and 8.)

Sections of the kidney disclosed a rather extensive arteriolonephrosclerosis.

The pyloric portion of the stomach and the adjacent duodenum showed a marked new formation of large tumor cells arranged in sheets, clusters, and glandular structures. The individual tumor cells were large, with round or oval nuclei which were markedly hyperchromatic. The cells had an abundant cytoplasm. A moderate number of atypical mitotic figures were noted. These tumor cells were also identified in large numbers in the lymphatics throughout the sections. They were similar in every respect to those which were found blocking the pulmonary arteries.

Thus, the outstanding and pertinent changes were marked atherosclerosis of the coronary arteries with thrombosis of the descending branch of the left coronary artery and a recent myocardial infarct adjacent to an organizing infarct which occupied a large area of the interventricular septum and the anterior wall of the left ventricle. This fresh infarct was apparently the immediate cause of death.

A clinically unexpected finding was a large foramen ovale. This defect obviously accounted for the marked right atrial and ventricular hypertrophy and the dilatation of the pulmonary artery. Although disease of the mitral valve is fairly commonly as-



Fig. 8. Hyaline thrombus in branch of pulmonary artery. Hematoxylin and eosin preparation, ×225.

radiate to the arms. The electrocardiogram is helpful in differential diagnosis, but, as will be seen, difficulties arise even in this area.

Distended neck veins may occur both in congestive heart failure and in emphysema without heart failure. Except with severe right ventricular failure of cor pulmonale, however, the venous distention of emphysema is most marked on expiration, and there is generally a distinct collapse on inspiration.[1]

Pulsus paradoxus which exceedes the normal upper limit of 8 mm.Hg may occur in emphysema and raise the possibility of pericardial effusion with tamponade or constrictive pericarditis. This is particularly so when one adds to the clinical picture distended neck veins, diminished heart sounds, palpable liver, and low voltage of QRS complexes on the electrocardiogram, all of which are common findings in emphysema or pericardial disease.

Difficulties in diagnosis may arise on *auscultation of the heart and lungs.* Because of the intervening overdistended lungs in emphysema, the heart sounds are frequently distant, and important murmurs may be missed unless auscultation is meticulously performed. Probably the most frequently missed significant murmur in this situation is that of aortic stenosis. Gallop rhythms (including both third and fourth heart sound gallops) which originate from the right side of the heart are common in emphysema and may be confused with those originating from the left side, where they have a different meaning. This problem is usually not difficult to settle, however, since gallops which originate from the right side are generally loudest near the sternum or in the epigastrium and are accentuated on inspiration and diminished on expiration. This is in contrast to those from the left side, which are loudest at the apex and have the reverse respiratory variation.[2] Pulmonary systolic clicks are common in emphysema with pulmonary hypertension and may be confused with triple rhythms of other varieties or with aortic systolic clicks. Differentiation from the latter is not difficult, however, in that pulmonary clicks, as opposed to the aortic type, are not well heard at the aortic area or at the apex, and they show more respiratory variation, especially becoming loudest on expiration.[2]

On auscultation of the lungs, one may detect both inspiratory and expiratory râles in either left ventricular failure or pulmonary emphysema. In addition to such characteristics as "moist" or "dry," a helpful clue to the cause of râles in difficult cases may be gained at times from the "shifting râles" sign.[3] Here, the patient sits with his legs off the edge of the bed while the chest is examined. He then lies to one side in the lateral decubitus position, with the legs still dependent. After he has been in this position for about 5 minutes, the râles due to congestive failure should clear in the uppermost lung, whereas those due to pulmonary disease tend to remain.

Laboratory studies

Difficulties in the interpretation of laboratory data not infrequently arise when emphysema and heart disease are under consideration. For example, a patient who presents with acute cor pulmonale from emphysema may have significant chest pain, altered electrocardiogram, and slightly elevated serum glutamic oxaloacetic transaminase (SGOT) activity, all causing possible confusion with myocardial infarction. The elevated SGOT in such cases is probably due to injury of the liver associated with anoxia and congestion.[4]

Interpretations of x-ray films may be difficult when emphysema and cardiac disease coexist, especially with reference to pulmonary vascular markings and enlargement of specific cardiac chambers.

The application and interpretation of pulmonary function tests is an extensive undertaking even when relatively isolated pulmonary disease is studied. When left ventricular failure or other cardiac disease is superimposed, suffice it to say that the problem is compounded, and pulmonary function tests are not only difficult to perform accurately but may be grossly abnormal and confusing.

Perhaps more emphasis should be given to the problems which arise in electrocardiography, since these are common and frequently met with in medical practice. Fig. 1 shows the typical electrocardio-

Selected problems in the management of emphysema complicated by heart disease in addition to cor pulmonale

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Patients with pulmonary emphysema frequently have significant degrees of associated heart disease, which raises problems both from the standpoint of diagnosis as well as treatment. For obvious reasons, the complicating heart disease is most frequently ischemic myocardial disease due to disease of the coronary arteries, but other types may be present. An interplay of considerations is apparent when the physician attempts to clarify the influence of emphysema on the diagnosis and treatment of heart disease, and, contrariwise, the influence of heart disease on the diagnosis and treatment of emphysema. In the discussions to follow, the term "heart disease" is used to imply disease of the heart other than cor pulmonale, but, obviously, cor pulmonale also may be superimposed. Discussions relative to pulmonary disease are directed primarily toward chronic diffuse obstructive pulmonary emphysema.

Problems in diagnosis

In the diagnostic evaluation of patients with cardiorespiratory symptoms, the physician must attempt to decide whether pulmonary disease or cardiac disease is responsible for the clinical manifestations, and, when the disorders coexist, he must delineate the contributions of each to the over-all clinical state.

History and physical findings

Dyspnea obviously is a symptom common both to patients with heart disease and those with pulmonary disease. It may occur at rest and on exertion, so that determination of its basis may be difficult. True paroxysmal nocturnal dyspnea and acute dyspnea associated with the production of pink frothy sputum denote pulmonary edema from failure of the left side of the heart. Orthopnea usually favors failure of the left side but there are frequent exceptions. Wheezing may be a prominent finding in primary heart disease ("cardiac asthma"), but it is usually more prominent and persistent in emphysema.

Chest pain and epigastric pain are not infrequent in patients with emphysema, especially when pulmonary arterial hypertension exists. The pain may occur on exercise and be relieved by rest or nitroglycerin. For obvious reasons, confusion with primary coronary artery disease is common. Generally, however, the pain of pulmonary hypertension is not so severe as coronary pain, and usually it does not

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graphic manifestations of cor pulmonale from emphysema developing in a 36-year-old man who was followed until his death at age 42. Through the years note the progressive changes in the electrocardiogram: right axis deviation; increase in amplitude of the P waves in Lead II; increased P waves, inverted T waves, increased R', and increased R/S ratio in Lead V_1; decreased R/S ratio and lower QRS complexes in Lead V_6. Right ventricular hypertrophy is certainly present. Note that in cor pulmonale the P waves are more prominent in Lead II (and Lead III) than in Lead I, in contrast to rheumatic heart disease (e.g., mitral stenosis), wherein severe right ventricular hypertrophy may occur but the P waves tend to be more prominent in Lead I (and Lead II) than in Lead III.

Fig. 2 is an example of a tracing which might be interpreted as showing significant S-T segment depression on exercise. In emphysema there is a tendency for the repolarization wave of the atria (T_a wave) to become prominent,[5] especially after exercise. In the tracing illustrated in Fig. 2, after exercise, the P waves become more prominent, as do the T_a waves (especially in Lead V_4); the latter cause an accentuated false depression of the S-T segment because of the superimposition of the T_a wave on the QRS and S-T segment. P waves and T_a waves also become prominent with increasing heart rates, and this factor must also be considered in the interpretation of such tracings. Although this patient may well have had significant coronary artery disease, the exercise test could not be used as strong confirmatory evidence for ischemic heart disease. A similar problem in another patient with emphysema is illustrated in Fig. 3. The effect of the T_a wave (shaded area) on the S-T segment in the post-exercise tracing is apparent. These tracings should be compared with that in Fig. 4, which was recorded in a patient with angina pectoris and an old myocardial infarction who developed chest pain during the two-step test. The gross similarity between Fig. 2 and Fig. 4 in the S-T segment depression in Leads V_4 and V_6 after exercise is apparent. However, in Fig. 4, although the changes are not marked after exercise, the S-T segment depression was not produced by a T_a wave.

The electrocardiogram in Fig. 5 shows large Q waves in Lead V_1 through Lead V_3 which were read as indicative of anterior myocardial infarction. A careful search at autopsy, however, revealed only moderate left ventricular hypertrophy, marked right ventricular hypertrophy, and very marked right atrial dilatation. There was no myocardial infarct. With marked right atrial dilatation, Q waves may develop in V leads on the right side, possibly because of associated rotation of the heart or other factors. Q waves in these leads, in the absence of infarction, may also occur in association with marked left ventricular hypertrophy and lead to difficulty in interpretation.[6] The mechanisms of such changes are unclear. Cardiac rotation or displacement, localized areas of myocardial hypertrophy, localized areas of electrical dysfunction, and other factors may be important either singly or in combination.

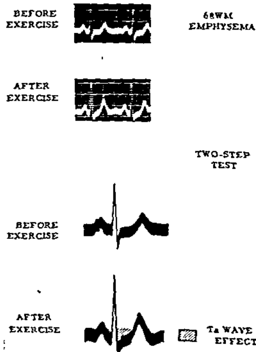


Fig. 3. Electrocardiogram from a patient with emphysema, demonstrating S-T segment depression after exercise due largely to prominent atrial repolarization waves. Consult text for details.

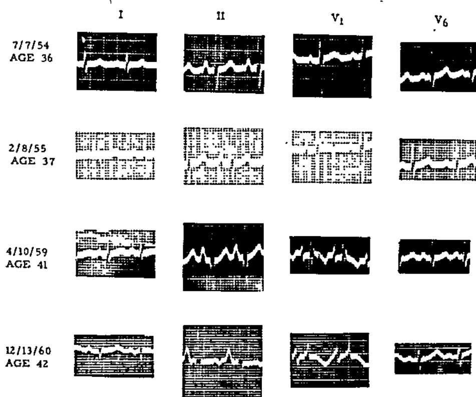


Fig. *1*. Series of electrocardiograms from a patient with autopsy-established diagnosis of severe bullous emphysema and cor pulmonale (marked right ventricular hypertrophy and dilatation and right atrial dilatation). Consult text for details.

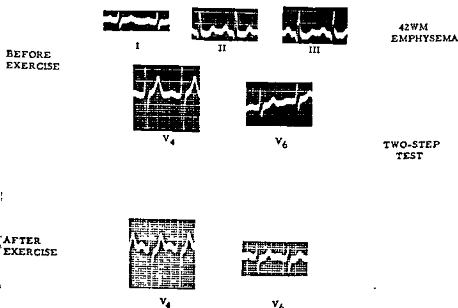


Fig. *2*. Electrocardiograms from a patient with emphysema, demonstrating post-exercise S-T segment depression due to prominent atrial repolarization waves. Consult text for details.

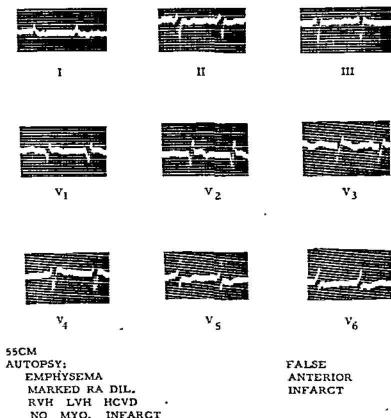


Fig. 5. Electrocardiogram from a patient with autopsy-proved emphysema, right ventricular hypertrophy, left ventricular hypertrophy, and marked right atrial dilatation. Systemic arterial hypertension had been diagnosed clinically. No myocardial infarction was found at autopsy, although the electrocardiogram strongly suggested the presence of an anterior lesion. Consult text for details.

both of which are commonly present in isolated left ventricular hypertrophy. As in this case, wherein left ventricular hypertrophy tended to mask changes in the right ventricle, the reverse may also occur when right ventricular hypertrophy effectively obscures left ventricular hypertrophy.[6]

Differential diagnosis of pulmonary emphysema from left ventricular failure

The foregoing points illustrate isolated problems that arise in the diagnostic evaluation of patients with heart disease and emphysema. Of practical importance is the differential diagnosis in a patient, usually a late middle-aged or elderly male, who presents with severe dyspnea, barrel chest, distended neck veins, palpable liver, hyperresonant percussion note over the chest, pulmonary râles, loud pulmonic second sound, and ankle edema. The important problem is to decide whether the findings are due to obstructive pulmonary emphysema or to left ventricular failure with simple coincident senile emphysema. The findings noted may be present in either disease state. The administration of morphine and oxygen are keystones in the treatment of the latter condition, but they may be lethal in the former. Thus, obviously, differentiation is of the utmost importance. It should be noted that, in some patients, left ventricular failure with "cardiac asthma" may respond quite well to epinephrine or aminophylline, as does the bronchial obstruction of pulmonary emphysema. "Therapeutic tests" may be not only dangerous but misleadir

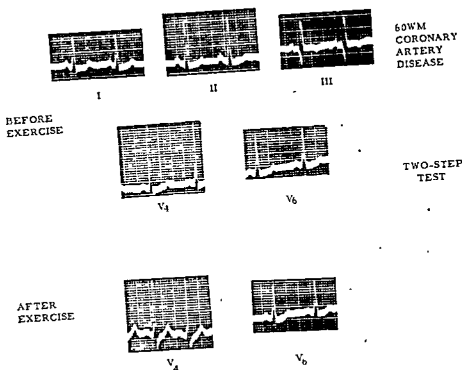


Fig. 4. Electrocardiograms from a patient with coronary artery disease, angina pectoris, and old myocardial infarction, demonstrating abnormal S-T segment depression after exercise. Compare with Figs. 2 and 3. Consult text for details.

Fig. 6 represents an example of a tracing which might be erroneously interpreted as showing a posterior-diphragmatic infarction because of large Q waves in Leads II, III, and aV_F. Such changes may occur in cor pulmonale, possibly because of cardiac rotational events or other mechanisms, as noted above. At autopsy this patient demonstrated only right ventricular hypertrophy, and no myocardial infarction was present. Perhaps a clue to the correct electrocardiographic diagnosis here was the absence of T-wave inversion in Leads II, III, and aV_F, plus evidence of right ventricular hypertrophy with T-wave inversion in Leads V_1-V_3 and the prominent P waves and T_a waves in Leads II and III.

Fig. 7 is an example of a tracing which was erroneously interpreted as showing right ventricular hypertrophy and cor pulmonale in a patient who had pulmonary emphysema. This error was probably made because of the R-R′ pattern in Lead V_1. At autopsy, however, this patient had a large high basal posterior infarct, and there was no right ventricular hypertrophy. The clue to the correct diagnosis in this case might have been the presence of abnormal S-T and T waves throughout, slurring and notching of the terminal portion of the QRS complexes in Leads II and III (infarct),[7] especially the Q_3T_3 pattern, and the absence of prominent P waves of cor pulmonale in Leads II and III.

Fig. 8 demonstrates how the presence of left ventricular hypertrophy (in this case due to systemic arterial hypertension) may mask the electrocardiographic diagnostic manifestations of right ventricular hypertrophy. This patient had severe bullous emphysema and cor pulmonale. Pulmonary function studies demonstrated a vital capacity of 50 per cent and a maximum breathing capacity of 20 per cent of normal. Chest roentgenograms and cardiac fluoroscopy showed prominent right ventricular and right atrial enlargement. The electrocardiogram demonstrates typical left ventricular hypertrophy, and the presence of right ventricular hypertrophy is not readily apparent. Perhaps the latter might be suspected because of the absence of left axis deviation and the absence of a sharp, rapid transition zone in the V leads,

magnitude to produce severe symptoms, one might expect a palpable cardiac apical impulse. In pulmonary emphysema, however, the hyperinflated lungs plus the low diaphragm tend to displace the cardiac impulse into the epigastrium, so that it is absent in the area of the fifth intercostal space in the mid-clavicular line. There are obvious exceptions to this rule, but this is frequently a helpful guide.

The detection of a left ventricular protodiastolic gallop and pulsus alternans, although these are frequently overlooked, is most helpful in the diagnosis of left ventricular failure, as may be the "shifting râles" sign noted above. Distended neck veins are nonspecific, but if the veins show obvious excursions, with distention on expiration and marked collapse on inspiration, then pulmonary disease is the favored diagnosis. It is traditional to assume that the presence of atrial fibrillation is unusual in uncomplicated cor pulmonale, and it favors left ventricular failure. There are exceptions to this, however.

If sufficient time is available, various laboratory procedures may be of help. From the chest x-ray films, one may detect either right or left ventricular enlargement and pulmonary findings compatible with either emphysema or pulmonary congestion.

The electrocardiogram is helpful especially if it clearly demonstrates either right ventricular hypertrophy or left ventricular hypertrophy. Furthermore, it may show electrical alternans, disturbances in cardiac rhythm, and myocardial ischemia, injury, or infarction, all of which tend to favor a diagnosis of left ventricular failure. It should be noted that with right ventricular hypertrophy, in addition to a diagnosis of cor pulmonale, one should consider mitral stenosis, especially if the elec-

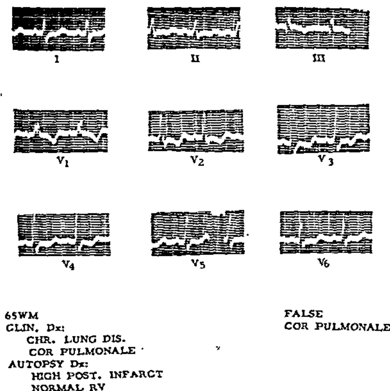
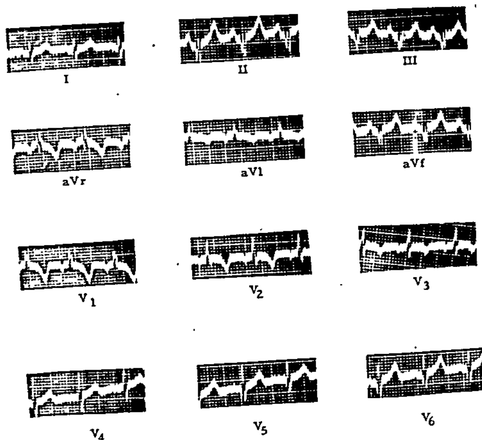


Fig 7 Electrocardiogram which was erroneously interpreted as showing right ventricular hypertrophy in a patient with chronic lung disease At autopsy this patient had a large high posterior myocardial infarction, but the right ventricle was normal. Co [illegible] text for details.



68CM
CLIN. DX:
EMPHYSEMA
COR PULMONALE
POST. INFARCT
AUTOPSY DX:
RVH
NO INFARCT

FALSE
POSTERIOR-
DIAPHRAGMATIC
INFARCT

Fig. 6. Electrocardiogram which might be erroneously interpreted as posterior-diaphragmatic myocardial infarction. Autopsy revealed emphysema and marked right ventricular hypertrophy but no myocardial infarction. Consult text for details.

The central problem is how to differentiate between these two radically different disease states that may present very similar findings. Specific details of the history and physical examination may be of considerable value.[8] A history of orthopnea and true paroxysmal nocturnal dyspnea inclines one toward the diagnosis of left ventricular failure, especially so if there is pink frothy sputum and an etiological reason for failure, such as systemic arterial hypertension, coronary artery disease, rheumatic valvular disease, etc. On the contrary, a history of prolonged exposure to respiratory irritants, including heavy smoking, with repeated and prolonged attacks of bronchitis with purulent sputum and recurrent episodes of progressive dyspnea for years, inclines one toward a diagnosis of primary pulmonary disease.

On physical examination the detection of a low, fixed diaphragm with limited excursion, inspiratory retraction of the rib margins (Hoover's sign), and hypertrophy of accessory respiratory muscles helps greatly in the diagnosis of significant pulmonary emphysema. The character of the apical impulse is additionally helpful. If left ventricular failure is of sufficient

may be helpful for one may be harmful for the other. Some of these problem areas are discussed below.

Sedatives, analgesics, and tranquilizers. The adverse effects of morphine in pulmonary emphysema are well known and should be remembered when emphysema coexists with disease which requires potent analgesics, e.g., acute myocardial infarction. Morphine may depress the respiratory center and precipitate carbon-dioxide narcosis in emphysema. Furthermore, it decreases the cough reflex, promotes pooling of secretions, and tends to produce bronchoconstriction. Dihydromorphinone (Dilaudid) is a potent analgesic which may have some advantage over morphine in such patients, in that in equianalgesic doses it has slightly less respiratory depressive action. Meperidine (Demerol), although less potent, is probably the safest in such cases and may be beneficial even in small doses (35 to 50 mg. intramuscularly). In large doses, meperidine may also cause respiratory depression, but it does not cause bronchoconstriction. However, the existence of any beneficial effect of meperidine over morphine when used in equianalgesic doses in such problems has been questioned recently.[9]

At times there are patients in whom there is no clear-cut satisfactory solution. One may not be able to administer enough analgesic to control severe pain without producing hazardous respiratory depression. Here one might give the above-mentioned narcotics in sufficient dosage to control pain and employ the narcotic antagonists, nalorphine (Nalline) or levallorphan (Lorfan), to alleviate respiratory depression. Evidence to date, however, suggests that narcotic antagonists adminis-

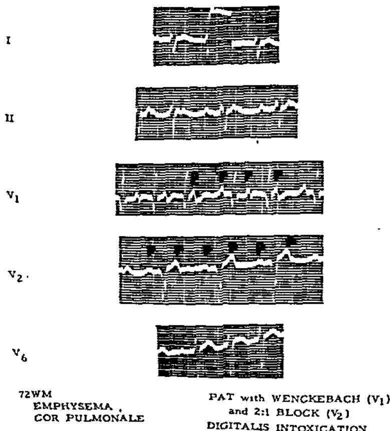


Fig. 9. Electrocardiogram from an elderly patient with severe emphysema and cor pulmonale, demonstrating paroxysmal atrial tachycardia with atrioventricular block from digitalis intoxication. Consult text for details.

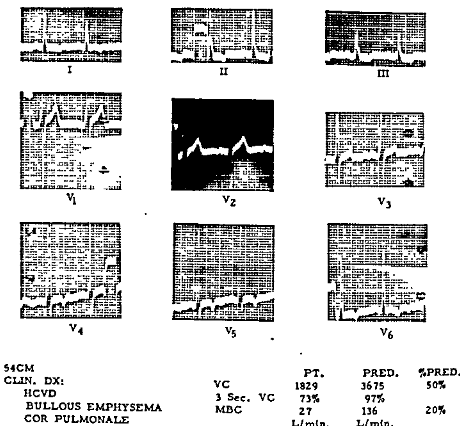


Fig. 8. Electrocardiogram and results of pulmonary function studies from a patient with hypertensive cardiovascular disease, severe bullous emphysema, and cor pulmonale. On the electrocardiogram, changes of left ventricular hypertrophy obscure those of right ventricular hypertrophy. Consult text for details.

trocardiogram shows broad, notched P waves in Leads I and II, or if it shows atrial fibrillation. In the presence of right axis deviation plus atrial fibrillation, one should carefully exclude mitral stenosis as the underlying heart disease.

Other laboratory tests are helpful. For the degree of symptoms, the arm-to tongue circulation time tends to be much longer in left ventricular failure than in emphysema. Arterial gas studies are revealing, in that for the degree of symptoms the oxygen saturation is generally decreased more in emphysema than in congestive failure; but, more helpful, the pCO_2 is increased in emphysema because of the retention of carbon dioxide, whereas in congestive heart failure it is normal or even low because of the hyperventilation associated with the dyspnea. In emphysema the arterial pH tends to be decreased (respiratory acidosis), whereas in congestive heart failure it tends to be normal or increased (respiratory alkalosis). Although not so reliable, one may gain some insight from the readily available carbon-dioxide combining power of venous blood, which would be expected to be high in significant obstructive emphysema.

Using the above-mentioned criteria, one can usually decide whether pulmonary disease or cardiac disease is primarily responsible for symptoms, or, when the two coexist, which accounts for what part of the clinical picture. One is then prepared to institute appropriate therapy.

Problems in treatment

When emphysema and heart disease coexist, several problems in therapy may arise. Of course, some therapeutic measures, such as the elimination of smoking and the treatment of infection, will be beneficial to both, but other measures that

Oxygen therapy. The well-known depressive effect of oxygen on the ventilatory drive in patients with emphysema and carbon-dioxide retention dictates caution when it is used. When oxygen is indicated in such patients, it is helpful to use graded and gradually progressive increases in flow rates, with particularly careful and close attention to and observation of the patient during the first 30 minutes of therapy. Through nasal catheter, one might start with a flow rate of 1 to 2 liters per minute during the first 24 hours, and then, gradually increase the flow by 1 liter per minute daily to a level of 4 to 5 liters per minute.[15] When a more acute need for oxygen in high concentration arises, the use of assisted mechanical ventilation is indicated.[16]

The beneficial effects of oxygen tents employed in patients with heart disease should not be forgotten. This benefit is derived largely through the provision of the cool, comfortable environment of the tent.[17] In patients with bronchopulmonary disorders the provision of clean, filtered, and adequately humidified air can be of benefit.

Phlebotomy. Phlebotomy may be a helpful measure both to patients with emphysema as well as to those with primary cardiac disease.[18] The commonly used indicator for phlebotomy is a hematocrit of approximately 55 per cent. At this level it is generally considered that the benefits of increased oxygen-carrying capacity are overcome by the adverse hemodynamic alterations coincident with polycythemia. It is apparent that some patients with emphysema do distinctly better with hematocrits of about 45 per cent, and, thus, phlebotomy might be used rather freely in such cases. Furthermore, in patients with superimposed angina pectoris, a lowering of the hematocrit level may produce an impressively favorable clinical response. In contrast to the use of phlebotomy in acute left ventricular failure (wherein one attempts to remove a relatively large amount of blood quickly), in emphysema the phlebotomies should be done slowly, with small amounts of blood (200 to 300 c.c.) being removed at one time until the hematocrit reaches the desired level. It is interesting that the hematocrit level may remain low for quite awhile after its initial lowering.

Cough suppressants. A good effective cough mechanism is helpful for patients with emphysema, but excessive coughing may add an extra burden to patients with coexisting heart disease. Thus, careful contol is indicated in this area. Sufficient hydration to help liquefy viscid secretions is a simple and effective but frequently overlooked therapeutic measure.

Diuretics. Diuretics are frequently used for emphysema with cor pulmonale or other forms of heart disease, but should be employed with caution, primarily because of their tendency to produce loss of potassium and hypokalemia as well as tenacious sputum. Electrolyte disturbances are especially likely to follow the use of the thiazide derivatives. Moreover, thiazides seem to have an arrhythmia-producing effect which is independent of obvious electrolyte alterations detectable by usual means.

Adrenal steroids. Adrenal steroids are frequently employed in the treatment of pulmonary emphysema, but caution is indicated here also when there is coexisting heart disease. This is because of the tendency of these agents to promote loss of potassium, retention of sodium, elevation of blood pressure, edema, and susceptibility to infection.

Hypokalemia. Hypokalemia is not infrequently observed during the treatment of pulmonary emphysema and may assume major importance, especially because of disturbances in cardiac mechanisms in patients who are receiving digitalis. During the respiratory acidosis encountered in severe emphysema, hydrogen ions displace intracellular potassium ions, which diffuse out and cause elevation of extracellular potassium. If this is reversed rapidly by treatment, e.g., with intravenous sodium or glucose, adrenal steroids, and diuretics, the urinary loss of potassium, plus replacement back into cells, may cause significant and rather sudden hypokalemia.[16] One should watch for this complication, which is certainly not infrequent.

Intravenous fluids. Intravenous fluids are frequently used in the treatment of severe emphysema to promote rehydration and to foster bronchial catharsis. In addi

tered simultaneously with narcotic analgesics cannot be relied on to prevent respiratory depression in patients with restricted pulmonary reserve.[10] This is a difficult procedure, satisfactory control is not easy, and the physician finds himself guessing in a complex clinical state. Perhaps the associated use of the comparatively safe new respiratory stimulant, vanillic diethylamide (Emivan), may be of benefit in these situations. It has been demonstrated to be an effective respiratory stimulant even in the presence of severe respiratory depression.[11] The drug's principal action is probably as a central respiratory stimulant, but secondary stimulation of respiration via the chemoreceptors of the carotid body has been proposed. Following its use, both volume and, to a lesser degree, rate of breathing are increased. This agent appears to hold real promise. Another drug, dichlorphenamide (Daranide), may prove to be of benefit in this area,[12] but results are not so impressive as with vanillic diethylamide and further evaluation is necessary. Nevertheless, dichlorphenamide is an interesting agent. It is a carbonic anhydrase inhibitor and causes a pronounced increase in urinary excretion of bicarbonate, producing a renal (metabolic) acidosis. When used in patients with chronic respiratory insufficiency, alveolar ventilation is increased, arterial oxygen saturation rises, and arterial pCO_2 falls. This action is through a rise in tidal volume, the stimulus for which appears to be a drop in extracellular pH (metabolic acidosis).[12] In addition to its effect on the loss of bicarbonate, the drug also causes increased renal loss of water, sodium, and potassium. Because of these effects, extreme care should be exercised when the drug is used in severely ill patients. Regardless of the pharmacologic means of therapy available, it is clear that certain patients will require assisted mechanical ventilation.

It is worth remembering that sedatives and tranquilizers, such as barbiturates and phenothiazine derivatives, are capable of depressing the respiratory center and, therefore, should be used with caution in patients with significant emphysema. The sedative of choice, in such instances, is probably chloral hydrate or paraldehyde.

Bronchodilators. Bronchodilators, a basic part of the treatment of pulmonary emphysema, are probably safe in most patients with coexisting heart disease, but caution is certainly indicated in those who have severe coronary artery disease or any cardiac disease with evidence of increased myocardial irritability. This is particularly so with ephedrine and epinephrine, which stimulate myocardial irritability and may provoke mechanism disturbances, including ventricular tachycardia and ventricular fibrillation. From this aspect, of the more potent bronchodilators, the safer drugs are probably isoproterenol (Isuprel), aminophylline, adrenal steroids, and choline theophyllinate (Choledyl). These drugs are also safer when elevation of the blood pressure is to be avoided. Isoproterenol, in addition to being a potent bronchodilator, is also a cardiac stimulant. It tends to stimulate the higher centers (sinoatrial node, atrioventricular node, bundle of His, bundle branches) to a greater degree, however, than it does the lower centers (ventricular myocardium), and thus has less tendency to produce ventricular tachycardia and fibrillation than does epinephrine.[13] It should be recalled that the frequently used drug, aminophylline, may increase myocardial irritability and cause peripheral vasodilatation with hypotension, particularly if given intravenously too rapidly. Methoxyphenamine (Orthoxine) is a safe bronchodilator for use in heart disease, but is not so effective as the drugs mentioned.

Antibiotics and anticoagulants. The frequent and recurring need for antibiotics in the management of emphysema is well known. This may cause considerable difficulty in the control of prothrombin-depressant anticoagulant therapy in patients on these agents for coronary artery disease or other cardiovascular disease. Antibiotics cause this difficulty by virtue of their ability to alter the vitamin-K-producing intestinal bacterial flora.[14]

Also, with reference to anticoagulant therapy, it is worth remembering that emphysema with severe cor pulmonale and right heart failure may be associated with a congested and anoxic liver and hepatic dysfunction. Anticoagulant therapy in such cases is obviously hazardous.

ings include diaphragmatic excursion, retraction of rib margins, type and location of the cardiac impulse, gallop rhythms, pulsus alternans, characteristic râles, mechanismal disturbances, and type of neck-vein distention. Laboratory data of importance are the electrocardiogram, chest x-ray film, circulation time, blood-gas determinations, and pulmonary function studies.

When emphysema and heart disease coexist, problems in treatment are compounded. Problem areas noted in this discussion include the use of: sedatives, analgesics, and tranquilizers; bronchodilators; antibiotics and anticoagulants; oxygen therapy; phlebotomy; cough suppressants: diuretics; adrenal steroids; fluid and electrolyte therapy; compression belts; antihypertensive agents and digitalis.

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to vascular overloading that may be produced in congestive failure, it should be remembered that, as seen above, intravenous glucose may lower serum potassium.

Abdominal compression belts. Abdominal compression belts may help some patients who have emphysema and may also aid some who have angina pectoris, especially those with pendulous abdomens. The belts may cause difficulty with varicosities and phlebitis of the lower extremities by impairing venous drainage. Compression belts are contraindicated in the presence of right ventricular failure with venous hypertension and hepatic engorgement.[16]

Antihypertensive agents. Some caution should be used with antihypertensive agents in the treatment of hypertension when significant pulmonary emphysema coexists.

Reserpine causes increased sensitivity to pressor amines and, therefore, should be used carefully in patients in whom such bronchodilator agents are employed. Moreover, reserpine may cause severe (central) respiratory depression, but this is usually only with relatively large parenteral doses.

Hydralazine (Apresoline) has at least a theoretical disadvantage in patients with emphysema, particularly those in whom allergic factors are prominent. This because of its antihistaminase activity, hich allows increased levels of histamine.

Like reserpine, the ganglion-blocking agents used in the treatment of hypertension also cause an increased sensitivity to pressor amines. This effect has been used therapeutically in selected cases to restore responsiveness to bronchodilators, but in hypertensive patients, or those with other cardiovascular disease, this use would be difficult to control and certainly not without danger. Furthermore, when one employs ganglion-blocking agents, he frequently uses pilocarpine or neostigmine to control undesirable side effects. The latter drugs are bronchoconstrictor agents and are not desirable in emphysema.

Digitalis and digitalis intoxication. Digitalis is frequently used in cor pulmonale of emphysema and is probably indicated when the right ventricle fails, even though the results are not spectacular. At this point it should be recalled that congestive failure of the right side of the heart is not the cause of the respiratory distress in patients with emphysema, but rather that the emphysema is the cause of the right-heart failure and respiratory distress Thus, the treatment of cor pulmonale is first the treatment of the pulmonary problem itself. "Pushing" digitalis is not indicated and may be dangerous. Digitalis intoxication is frequently seen in the management of emphysema, probably for three basic reasons. First, there is an erroneous tendency to progressively increase digitalis dosage to control edema and lessen dyspnea. Secondly, through mechanisms indicated above, the development of hypokalemia is frequent in these cases, and this tends to augment digitalis intoxication. Thirdly, in general, because the patients are in the older age groups, there is frequently an increased sensitivity to digitalis.

It is interesting that a manifestation of digitalis intoxication which is being recognized with increasing frequency in emphysema is the so-called paroxysmal atrial tachycardia with atrioventricular block (Fig. 9).[19] This is so probably because of an increased awareness of this disorder, plus its intimate association with potassium depletion.[20]

Summary

Emphysema is frequently complicated by the presence of heart disease other than cor pulmonale. This association raises many problems in diagnosis and treatment.

One is frequently confronted with a patient complaining of dyspnea who is noted to have a barrel chest, distended neck veins, palpable liver, hyperresonant percussion note, pulmonary râles, loud pulmonic second sound, and ankle edema. These findings might be due either to diffuse obstructive pulmonary emphysema or to left ventricular failure with simple, coincident, nonsymptomatic senile emphysema. The differentiation is obviously important.

In this discussion, clinical guide lines are presented which are helpful in making this distinction. Pertinent points in the history include orthopnea, paroxysmal nocturnal dyspnea, exposure to respiratory irritants, and the duration and course of the symptomatology. Helpful physical find-

white women who died in less than 1 hour, 422 men and 32 women showed severe coronary atherosclerosis. When death occurred after 1 hour or more, the finding of severe coronary atherosclerosis was less common. In only 14 of the 584 cases of witnessed sudden death was there cerebral hemorrhage.

Among 2,030 autopsied cases of sudden and unexpected natural death reported on by Helpern and Rabson,[3,4] there were 912 cases of disease of the heart and great vessels, and in 617 (67.7 per cent) of this group death was due to occlusive coronary atherosclerosis. In 75 per cent of these cases there were no fresh acute occlusive lesions in the coronary arteries. Eighty per cent of the patients with coronary artery disease died virtually instantly.

In the discussion of these data presented by Dr. Paul D. White and Dr. John H. Turner in Moscow on May 17, 1961, at Professor A. Myasnikov's Institute of Therapy, observations were added by Professor Lecomsky and Dr. Smoljaninov.

Professor Lecomsky noted that of 3,484 autopsied medicolegal cases of nontraumatic sudden death, 2,411 were due to cardiovascular disease; in the great majority the diagnosis was either hypertension or atherosclerosis. There were 431 cases of myocardial infarction, 24 with cardiac tamponade, 122 with cerebral hemorrhage associated with hypertension, and 103 with cerebral hemorrhage not associated with hypertension. The degree of suddenness of these deaths was not recorded.

Dr. Smoljaninov had studied many cases of sudden death, 90 per cent of which were due to cardiovascular causes, and, in turn, 90 per cent of these showed marked atherosclerosis of the coronary arteries.

Dr. Andrus raised the question of investigation of the cardiac mechanism of sudden death, that is, the occurrence of ventricular fibrillation versus cardiac standstill, which has, of course, important implications in the matter of resuscitation, closed-chest massage, external defibrillation, and the external cardiac pacemaker, as well as direct resuscitation with the chest open.

Thus, instantaneous death appears to be a complication in the great majority of cases of occlusive coronary atherosclerosis, but further research is needed to determine the degree of suddenness of "sudden death."

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Terminology of the second heart sound

The traditional terminology employed in reference to examination of the heart uses the expressions A_2 to refer to the second heart sound in the second intercostal space to the right of the sternum, and P_2 to refer to the second heart sound in the second intercostal space to the left of the sternum. These expressions have been used and taught with the rationale that closure of the aortic valve and closure of the pulmonary valve were mainly responsible for the second heart sound in these respective areas. Apparently, these events were formerly thought to occur simultaneously or nearly simultaneously. In recent years, with improvements in the examination of the heart and in the knowledge of cardiac hemodynamics, it has been more generally appreciated that the second heart sound (S_2) is normally composed of two components, of which the first component is normally produced by closure of the aortic valve and the second component is produced by closure of the pulmonary valve a short time later. In phonocardiographic studies, for example, the expression A_2 is used to refer to the closure of the aortic valve itself, wherever the sound may be recorded, and P_2 is used to refer to the closure of the pulmonary valve itself, wherever this sound may be recorded. In order to improve the accuracy of expression and communication and the understanding of cardiovascular hemodynamics by all persons performing and describing an examination of the heart, and to avoid describing physiologically unlikely events, such as P_2 being "split," it would appear advantageous to change the previous clinical use of the expressions A_2 and P_2 to conform with current knowledge. Thus, A_2 should refer to closure of the aortic valve, and P_2 should be used in reference to closure of the pulmonary valve, wherever these sounds are heard. The expression "A_2 greater than P_2" should be employed only when it is possible to hear both components of the second heart sound (S_2) and to determine that the aortic component of the second sound (A_2) is greater than the pulmonary component (P_2). In patients with

A note on the discussion of nontraumatic sudden death by American and Soviet cardiologists in Moscow in May, 1961

Among the cardiovascular subjects considered in Moscow in May, 1961, at the third series of official meetings between the Soviet and American cardiologists initiated by the agreement signed by the U.S.A. and the U.S.S.R. in November, 1959, there was a discussion of sudden death not caused by trauma.

For many years, sudden deaths which were not the result of trauma have quite naturally attracted great interest throughout the world as well as among the medical profession. Pliny the Elder in the first century A.D. wrote a chapter on sudden death in his work on *Natural History*. He cited by name important Romans—senators, physicians, and business men—who dropped dead in the course of their daily activities, but since there were no autopsies then to explain such deaths, they were usually ascribed to an act of the gods.

Throughout the Middle Ages, in manuscripts and in early printed books, as well as among the writings of the medical authorities in the seventeenth and eighteenth centuries, there were chapters on sudden death, and in 1707, an entire volume was devoted to the subject by the great Italian physician, Lancisi, who, at the request of the Pope, performed autopsies on Romans who died suddenly during the winter of 1705-1706, and described the findings in the book entitled *De Subitaneis Mortibus*. A natural cause for death was found in every case, and Lancisi referred especially to diseases of the blood vessels with obstruction therefrom of the free flow of blood.

One of the great difficulties rarely clarified has concerned the degree of suddenness of sudden death. Inasmuch as this time element is very important from the standpoint of cause, we have attempted an analysis as to causation in relation to time intervals. Recent autopsy data secured at the Office of the Chief Medical Examiner of the City of New York give the following information.

In the first series of cases, which consisted of 78 witnessed deaths of occlusive coronary artery disease, deaths were instantaneous in 49 cases. At autopsy, these cases, in addition to occlusive coronary atherosclerosis, showed coronary thrombosis in 7 (2 fresh and 5 recent) and only severe occlusive coronary atherosclerosis without recent or fresh thrombosis in 42. In 14 others of the 78 cases, death occurred within 30 minutes of the acute illness, and in the remaining 15 it occurred during the interval between 30 minuts and 6 hours.

In another series autopsied during a previous period, there were 70 cases of sudden natural witnessed deaths, and in 27 of these, death appeared to be instantaneous. Twenty-three of these 27 showed marked occlusive atherosclerosis, 3 showed chronic rheumatic valvular disease, and 1 showed simple cardiac hypertrophy. Death in 29 cases in this series occurred within 30 minutes, and in another 14, it occurred in the interval between 30 minutes and 6 hours. Thus, it seems quite clear from even these small samples that instantaneous death, that is, within seconds, is preponderantly the result of serious coronary atherosclerosis, generally without fresh or recent thrombosis. The deaths which occurred within 30 minutes were found to be due to a variety of causes, and included 13 cases of occlusive coronary artery disease and 1 case of cor pulmonale. The remainder consisted of spontaneous rupture of the aorta with dissecting aneurysm and hemopericardium, rupture of an aortic aneurysm into a bronchus, spontaneous cerebral hemorrhage, spontaneous subarachnoid hemorrhage, and nontraumatic pulmonary embolism derived from thrombosis of hypogastric veins in association with a large fibroid uterus and lobar pneumonia.

The 14 cases in the series in which death occurred between 30 minutes and 6 hours after the onset of the acute illness included, at autopsy, 8 cases of occlusive coronary atherosclerosis, 2 of cerebral hemorrhage, 3 of subarachnoid hemorrhage, and 1 of epilepsy.

Crawford, Dexter and Teare[1] reported a study of pathology of the coronary arteries in sudden death, using injection studies and microsection by the semiserial section method. A comparison by age was made in 75 cases, and in every case the lesion was that of marked segmental atherosclerosis of the coronary arteries. Thrombosis, when it occurred, was present only when the lumen was narrowed by 30 per cent or more.

Spain and Bradess[2] made a report on the frequency of sudden death in 1,329 consecutive autopsies. Three categories of time were listed: (1) less than 1 hour, (2) 1 to 3 hours, and (3) sudden without specification. Of 463 adult white men and 66 adult

The ancillary laboratory methods are very disappointing in establishing the correct diagnosis. The electrocardiogram usually shows findings which are indistinguishable from those which occur in mitral stenosis, namely, the presence of left atrial and right ventricular hypertrophy. Conventional radiography is likewise of no help in establishing the diagnosis of atrial myxoma. Occasionally, the finding of a small left atrium in the presence of severe "mitral stenosis" should raise this diagnostic possibility.

Cardiac catheterization reveals data which are typical of mitral stenosis with elevated pulmonary arterial and pulmonary arterial wedge pressures and a low, fixed cardiac output. Catheterization of the left side of the heart by any technique may be dangerous, since portions of the tumor may be dislodged and cause peripheral embolization. Left atrial pressure contours reveal high v waves and ordinarily do not help in distinguishing myxoma from mitral stenosis and regurgitation. However, one report of catheterization of the left atrium by the transbronchial method did disclose significant changes in the pressure and contour of the left atrial curves, depending upon the location of the catheter in relation to the tumor.[4]

The most reliable method of diagnosing left atrial myxoma is angiocardiography. The tumor produces a round, centrally located defect in the left atrium. Thrombi, on the other hand, have an irregular outline and usually hug the posterior atrial wall. Angiocardiography carries a small but definite risk, and, furthermore, it is impractical to perform this test on every patient with mitral stenosis. From what has been said, it is evident that left atrial myxoma may be suspected under the following circumstances, which also serve as indications for the performance of angiocardiography: (1) a history of unexplained syncope, especially if it occurs with signs and symptoms of mitral stenosis; (2) the appearance of previously undiscovered mitral murmurs in the presence of intractable congestive heart failure; (3) atypical auscultatory findings of mitral stenosis, consisting of changing intensity of the presystolic murmur, atypical location of the opening snap, murmurs which are not so loud as expected from the height of the atrial or pulmonary arterial wedge pressure, and variability in the intensity and character of the murmurs with a change in body position, (4) the occurrence of embolic phenomena in the presence of normal sinus rhythm, and (5) a triad of anemia, elevated sedimentation rate, and fever in the absence of rheumatic fever or subacute bacterial endocarditis.

This discussion would not be complete without mentioning right atrial myxoma. Isolated rheumatic tricuspid stenosis is rare, and if cardiac catheterization reveals a diastolic filling gradient across the tricuspid valve with normal pulmonary arterial wedge pressure, right atrial myxoma must be considered.

In closing, it should be noted that the origin of myxoma is obscure, and whether it is a true tumor or the myxomatous degeneration of a thrombus still remains to be established.

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The bronchopulmonary anastomoses

The existence of anastomoses between the greater and lesser circulations is at the present time beyond discussion.

There are essentially two major groups of anastomotic vessels, namely, the connection from the bronchial arteries to the pulmonary veins,[1] and that from the pulmonary artery to the bronchial veins.[2] Evidence of such shunt pathways is deduced from experiments in animals. Although this is true for the normal dog, attempts to measure this shunt flow in man have been carried out only sporadically.[3-5]

Recently, some modifications of the dye-dilution technique were tried on human beings,[6,7] and the findings have given rise to some interesting points which are worthy of further consideration.

1. Venous admixture. The lung tissue has a very low rate of oxygen consumption.[7] Blood from the bronchial vessels which is diverted to oxygenated pulmonary venous flow produces a decrease of 0.5 per cent in arterial oxygen saturation. This represents a meager percentage in normal conditions.

In some chronic lung diseases accompanied by anoxemia (tuberculosis,[8] emphysema,[9] embolism,[10] bronchiectasis[3]) there is an increase in bronchopulmonary arterial anastomoses, but the effect on venous admixture is minimized by the shift in arterial oxygen saturation to the steep portion of the oxihemoglobin dissociation curve.

2. Systemic-to-pulmonary shunt. The output of the left ventricle is greater than that of the right

septal defect, for example, it may be possible [to dif]ferentiate the two components of the second [heart s]ound (S_2) adequately enough to state that [P_2] (referring to the intensity of the second com[ponen]t of the second heart sound produced by [clos]ure of the pulmonary valve) is greater than A_2" (referring to the first component of the second heart sound produced by closure of the aortic valve) Although the value of describing the relative intensity of the second heart sound(s) in the second intercostal space to the right and left of the sternum has been overemphasized previously, traditions die slowly, and a descriptive method should be available for use when desired. The most precise and simple would be merely to state that the second heart sound(s) in the second right intercostal space was greater (or less) in intensity than the second heart sound(s) in the second left intercostal space. This could be abbreviated as $S2_{2R} > S2_{2L}$ or $S2_{2R} < S2_{2L}$, in which the subscripts 2R and 2L refer to the second intercostal space to the right and to the left of the sternum, respectively. This system can also be used with appropiate symbols to describe and localize heart sounds in other areas.

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The diagnosis of atrial myxoma

Myxoma of the left atrium, the most frequently occurring cardiac tumor, presents a variable and often bizarre clinical picture. Although it most frequently simulates mitral stenosis in its clinical manifestation, it may masquerade as bacterial endocarditis, pulmonary and cerebral embolism, or a rapidly progressive, intractable heart failure of undetermined etiology

By virtue of anatomic location, the hemodynamic abnormalities caused by left atrial myxoma are identical with those produced by mitral stenosis. This makes the differentiation between the two very difficult. The majority of atrial myxomas have been diagnosed during the course of a proposed commissurotomy for alleged mitral stenosis Since the successful removal of the tumor and, therefore, the survival of the patient depend upon the use of open-heart surgery, the necessity for a correct preoperative diagnosis is self-evident

In hunting for the diagnostic clues of atrial myxoma it is necessary to sift information from history, physical examination, and ancillary laboratory methods. Since only about one half of the patients with mitral stenosis give a history of antecedent rheumatic fever, the failure to obtain such a history is of little help in ruling this diagnosis in or out. Nor does a positive history establish the diagnosis of mitral stenosis, because some patients with atrial myxomas give a history of antecedent arthralgias which can readily be mistaken for the rheumatic state. On the other hand, syncopal attacks, although uncommon, are nevertheless of diagnostic significance, since they are quite characteristic of myxoma. Such episodes are rare in mitral stenosis.[1]

Physical examination and auscultation in cases of left atrial myxoma usually reveal the classic findings of mitral stenosis. The first sound at the apex is markedly accentuated and delayed. In the mitral area a rumbling diastolic murmur with presystolic accentuation is commonly heard. Occasionally, when the tumor protrudes through the mitral valve, a systolic blowing mitral regurgitation murmur may be present. The pulmonic component of the second sound at the base of the heart is accentuated in patients with pulmonary hypertension. In this group it is often followed by the classic Graham Steell murmur of pulmonary insufficiency. An opening snap is frequently heard, the origin of which, in the presence of a normal mitral valve, depends solely on the high atrioventricular filling gradient.[2] Under this circumstance the mitral valve opens abruptly, with the production of an audible sound. It is also possible that the stream of blood that rushes from the atrium into the ventricle causes the tumor to strike against the mitral valve leaflets and produces audible vibrations. Additional auscultatory findings consist of a tricuspid systolic murmur of varying intensity, which often becomes louder with inspiration. In the presence of severe congestive heart failure this murmur may have a peculiar musical quality.

Careful auscultation and phonocardiography may reveal deviations from the classic findings of mitral stenosis which are suggestive of left atrial myxoma. These include the following: (1) diastolic and presystolic murmurs which are not ao loud as might be expected from the hemodynamic derangements and the severity of the disease; (2) marked change in the character and intensity of the murmurs induced by shifts in body position and variability of murmurs from one examination to another; (3) atypical location of the opening snap (whereas in mitral stenosis the opening snap is best heard in the third or fourth intercostal space at the left sternal border, in atrial myxoma it may be heard over the entire precordium or be localized in the fifth intercostal space at the anterior axillary line); and (4) the appearance of previously undiscovered murmurs of mitral stenosis in patients with congestive heart failure.

In patients with mitral stenosis and atrial fibrillation, peripheral embolization is a frequent phenomenon. When embolization occurs in the presence of normal sinus rhythm, however, atrial myxoma must be seriously considered. Furthermore, anemia, an elevated sedimentation rate, and fever may occur with tumor embolization, thus simulating bacterial endocarditis or acute rheumatic fever.[2]

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